Southern Medical Journal

JOURNAL OF THE SOUTHERN MEDICAL ASSOCIATION

DECEMBER, 1957 Volume 50 Number 12

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DECEMBER 1957

VOLUME 50 NUMBER 12

Southern Medical Journal

JOURNAL OF THE SOUTHERN MEDICAL ASSOCIATION

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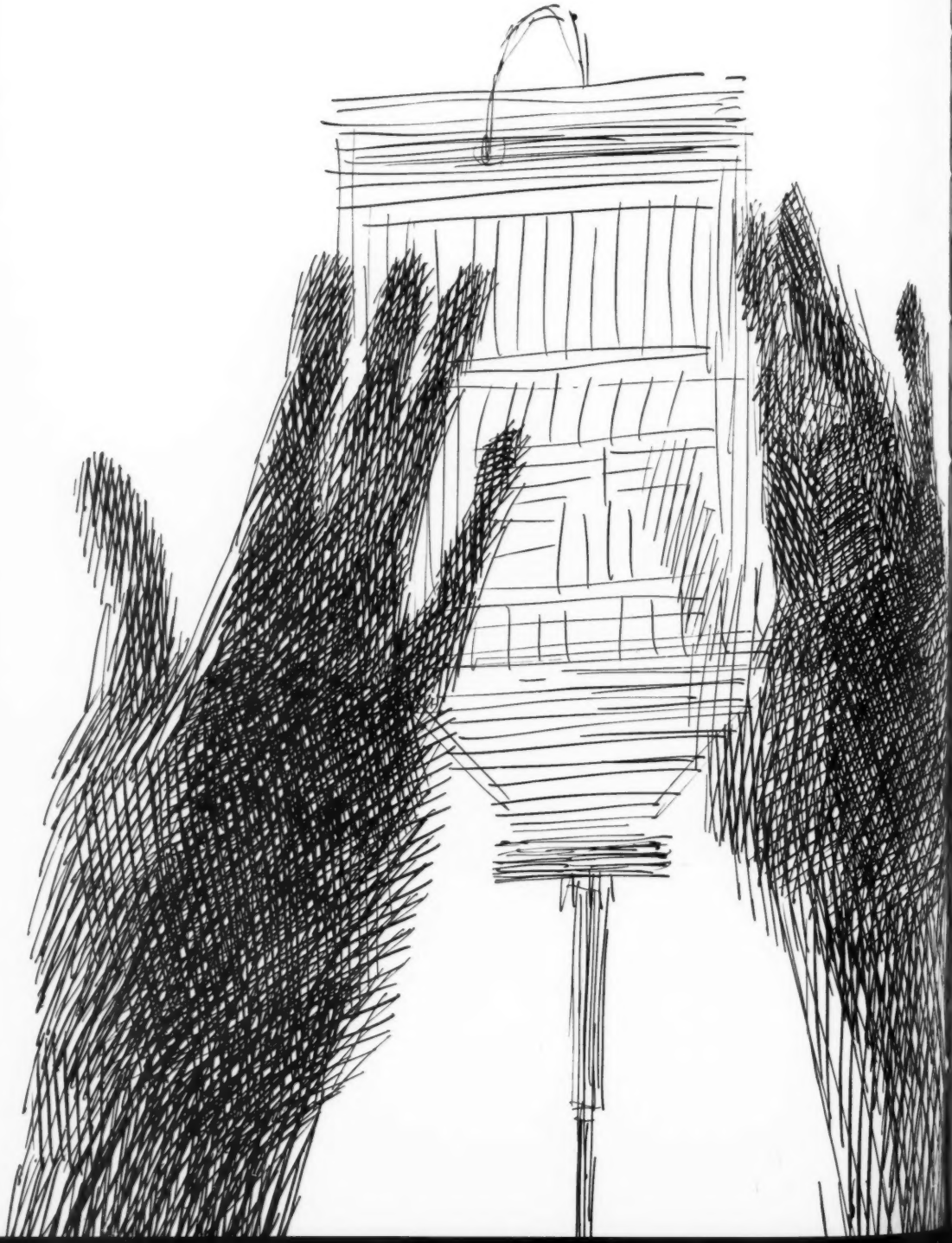

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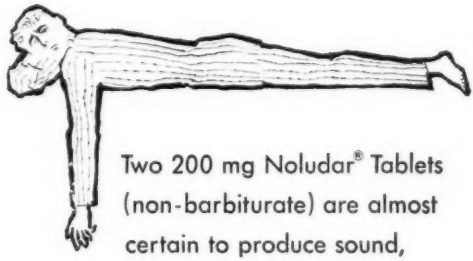
feeling 

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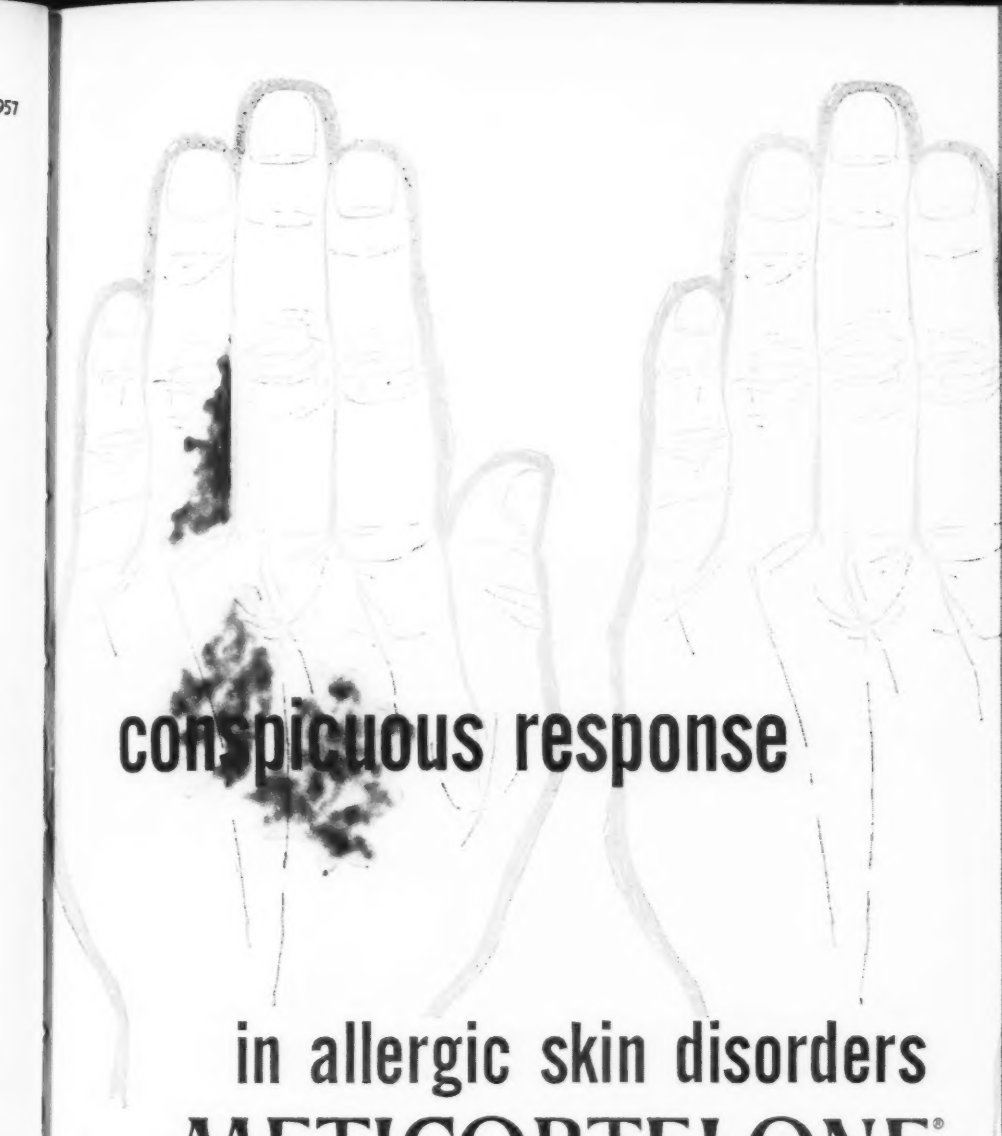

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1. Goodman, L. S. and Gilman, A.: *The Pharmacological Basis of Therapeutics,* Ed. 2, The Macmillan Co., New York, 1955, p. 856.

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Lewis, H. H.: Frumess, G. M., and Henschel, E. J.: Rocky Mountain M. J. 54:806 (Aug.) 1957.

"Results of treatment with oleandomycin-tetracycline of 50 infections [mostly respiratory] due to resistant organisms and 40 infections [respiratory, skin, urinary infections] due to sensitive organisms are very encouraging. In some of these patients, [Signemycin] was lifesaving, and in others surgery was made unnecessary. This confirms other reports."

Shubin, H.: Antibiotic Med. & Clin. Therapy 4:174 (March) 1957.

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Levi, W. M., and Kredel, F. E.: J. South Carolina M. A. 53:178 (May) 1957.

Of 50 patients with various infectious processes, 26 had not responded to previous antibiotic therapy. With Signemycin "Ninety-six per cent of the mixed infections were clinically controlled. . . . and in none of the cases was there any reason to discontinue the drug."

Winton, S. S., and Chesrow, E.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 55.

Signemycin in 79 patients with severe soft tissue infections: "The average response of these cases was excellent and inflammatory symptoms subsided with almost uniform rapidity....The magnitude and incidence of surgical intervention was reduced....Side reactions were minimal. . . ."

LaCaille, R. A., and Prigot, A.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 67.

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Frank, L., and Stritzler, C.: Antibiotic Med. & Clin. Therapy 4:419 (July) 1957.

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Loughlin, E. H., and Mullin, W. G.: Antibiotics Annual 1956-1957, New York, Medical Encyclopedia, Inc., 1957, p. 63.

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suggestion:

Upon retiring, a TRICHOTINE douche followed by a VACID suppository provides maximum effectiveness and 24-hour pH control.

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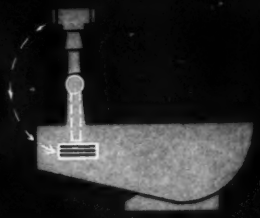

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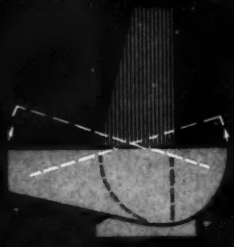

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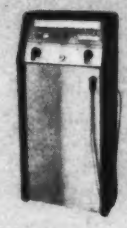

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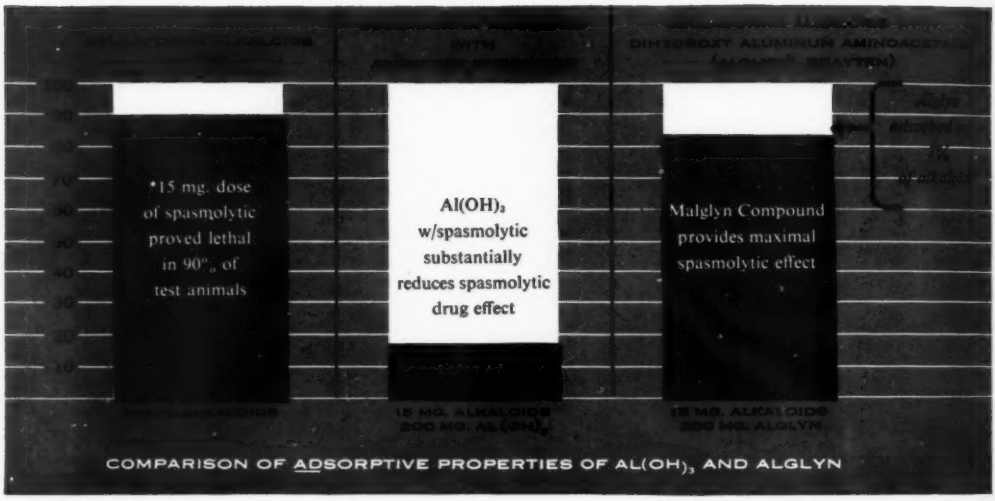
Here's a startling adsorption story involving simultaneous administration of antacid and spasmolytic drugs!


*15 mg. dose of spasmolytic proved lethal in 90% of test animals
Al(OH)3 w/spasmolytic substantially reduces spasmolytic drug effect
Malglyn Compound provides maximal spasmolytic effect
COMPARISON OF ADSORPTIVE PROPERTIES OF AL(OH)3 AND ALGLYN

The above laboratory study clearly indicates that the antacid ALGLYN, contained in the MALGLYN formula, does not materially interfere with the therapeutic effectiveness of its contained belladonna alkaloids. On the other hand, the marked *ad*sorptive properties of aluminum hydroxide renders its combination with belladonna alkaloids both uneconomical and therapeutically unreliable.

For both rapid and prolonged antacid effect, with consistently effective spasmolytic and sedative action, rely upon MALGLYN for treatment of peptic ulcer and epigastric distress.

each tablet contains

dihydroxy aluminum aminoacetate N.N.R.	0.5 GM
belladonna alkaloids (as sulfates)	0.162 MG.
phenobarbital	16.2 MG.

Also supplied: ALGLYN® (dihydroxy aluminum aminoacetate, N.N.R. 0.5 Gm per tablet). BELGLYN® (dihydroxy aluminum aminoacetate, N.N.R., 0.5 Gm. and belladonna alkaloids, 0.162 mg. per tablet).

Specialities for the Medical Profession only

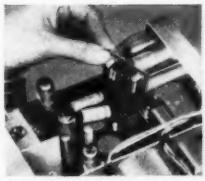
BRAYTEN PHARMACEUTICAL COMPANY

CHATTANOOGA 9, TENNESSEE

SANBORN MODEL 300

VISETTE

ELECTROCARDIOGRAPH



modern components, construction give greater durability

The transistors, printed wiring panels and smaller galvanometer that help make the new 18 pound VISETTE ecg the size of a brief case also make possible another — and equally important — advantage: *ruggedness.* Metal-encased transistors, most of them smaller than a pencil eraser, are used in place of many vacuum tubes in the Visette circuit; they can withstand extreme jolts, jars and vibration without damage. And instead of dozens of connections which would ordinarily be made with wire, conductive paths are *printed* on small, rigid phenolic panels. The Visette's direct-writing galvanometer, too, is designed for increased resistance to both physical and electrical hazards. The rigid metal frame and chassis, to which all units are anchored, is then housed in an outer case of high impact Royalite, reinforced with metal strips at points of greatest strain.

Here is *true* portability — a carefully designed combination of *light weight* (that every nurse and technician will appreciate); *small size* (that requires the same space on your desk as a letterhead); and *ruggedness,* that assures continued accuracy of operation after countless trips in your car, on hospital and house calls, wherever your Visette is required. Handy "companions" for the Visette include a protective vinyl Weather Cover, and a compact, attractive table for office use of the Visette.

You *can* take it with you — *with confidence.*

18 lbs.
TRANSISTORIZED
$625 del.

An informative four-page folder describes and pictures all major characteristics of the new Model 300 Visette electrocardiograph. Copies available on request.

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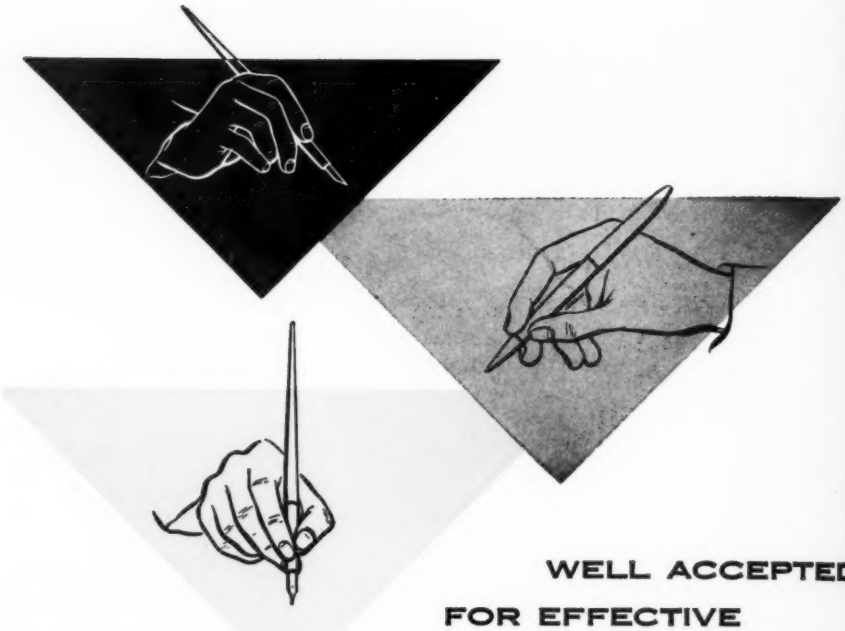
MEDICAL DIVISION

175 Wyman St., Waltham 54, Mass.



WELL ACCEPTED
FOR EFFECTIVE
COUGH RELIEF

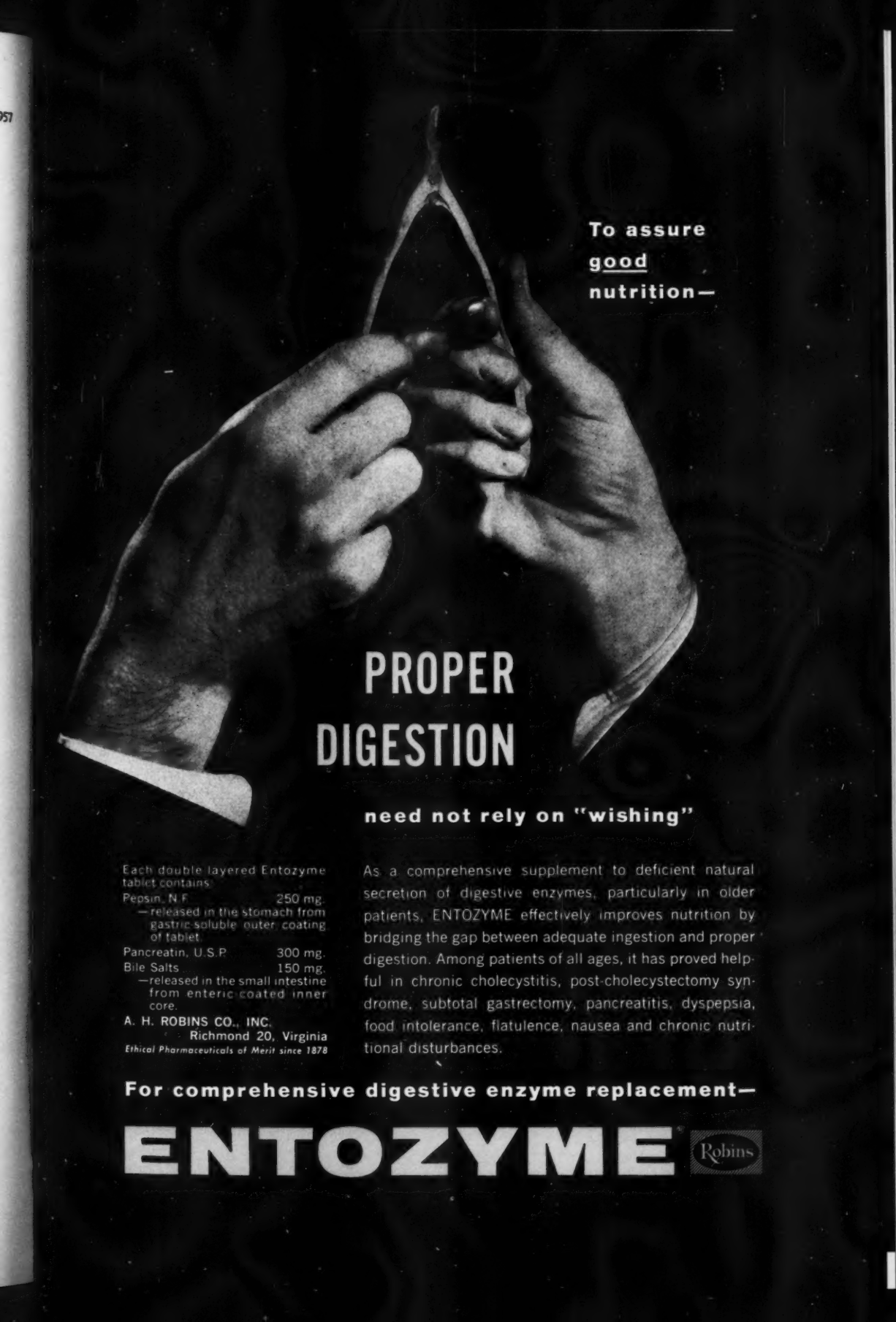
pyraldine®

and pyraldine® No. 2

Each fluidounce of **bright yellow PYRALDINE** *contains:*

Dihydrocodeinone bitartrate	1/6 gr.	*Controls, without completely suppressing, the cough reflex*
Pyra-Maleate® (Brand of Pyrilamine Maleate)	75 mg.	*Suppresses allergic manifestations; provides mild local anesthetic effect in the throat*
Ammonium Chloride	6 gr.	*Liquefy mucus and facilitate expectoration*
Citric Acid	5 gr.	
Amber PYRALDINE No. 2 — the basic Pyraldine formula plus Phenylephrine Hydrochloride per fluidounce	30 mg.	*For added mucosal decongestion*

VANPELT & BROWN, INC., Richmond, Va.


To assure good nutrition—
PROPER DIGESTION
need not rely on "wishing"
Each double layered Entozyme tablet contains:
Pepsin, N.F. 250 mg.
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—released in the small intestine from enteric coated inner core.
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As a comprehensive supplement to deficient natural secretion of digestive enzymes, particularly in older patients, ENTOZYME effectively improves nutrition by bridging the gap between adequate ingestion and proper digestion. Among patients of all ages, it has proved helpful in chronic cholecystitis, post-cholecystectomy syndrome, subtotal gastrectomy, pancreatitis, dyspepsia, food intolerance, flatulence, nausea and chronic nutritional disturbances.
For comprehensive digestive enzyme replacement—
ENTOZYME
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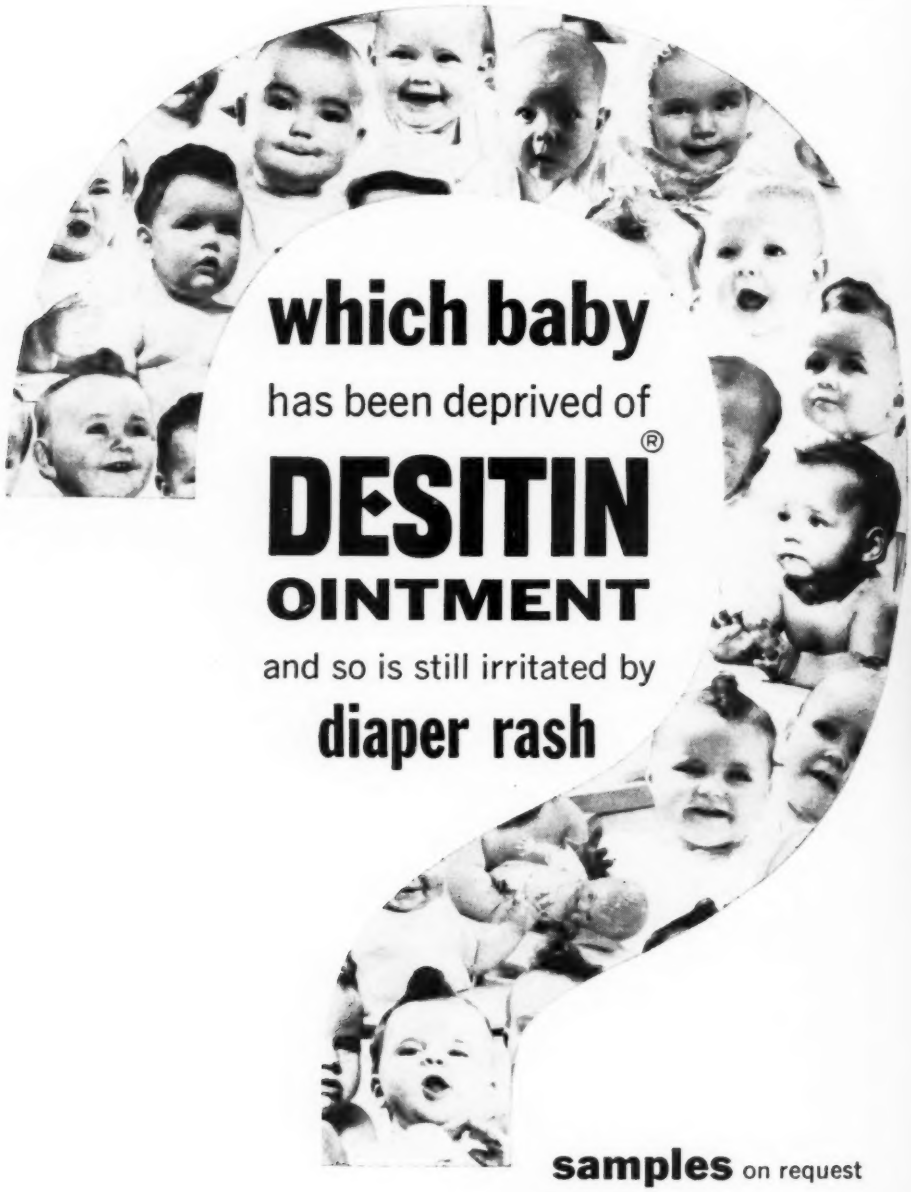

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in the eyes of industry
more visible results...
more man-hours saved

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OPHTHALMIC SUSPENSION

(prednisolone acetate and sulfacetamide sodium)
antiallergic...antibacterial...anti-inflammatory

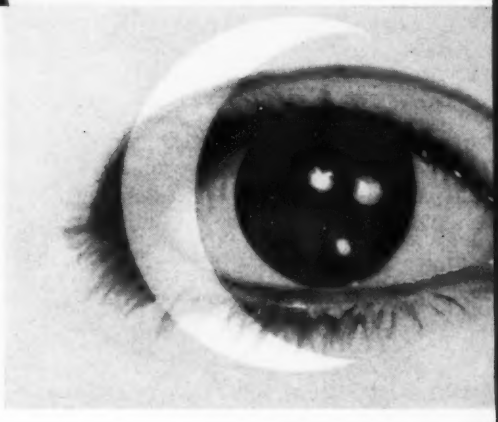
VISIBLE RESULTS, MORE QUICKLY—Prednisolone, the corticosteroid component in METIMYD, acts more rapidly on topical application in the eye than either hydrocortisone or cortisone.[1]

MORE MAN-HOURS SAVED—Sulfacetamide sodium, the sulfonamide component in METIMYD, possesses unsurpassed antibacterial activity for ophthalmic use. In extensive clinical use it has reduced the number and duration of return visits,[2] thereby saving precious man-hours.

and especially for nighttime use and as a protective dressing

METIMYD OINTMENT with NEOMYCIN

"Meti"*steroid plus potentiated antibacterial action



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2. Kuhn, H. S.: Tr. Am. Acad. Ophth. 55:431, 1951.

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MM-J-387

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New Chemotherapy of RHEUMATOID ARTHRITIS

Long-term studies in this country and abroad have shown that the antimalarial ***ARALEN*** *phosphate produced major improvement in 72% of 294 cases of rheumatoid arthritis. Aralen was often successful where other agents failed. Remissions often persisted for many months after therapy had been discontinued.*

JOINT EFFECTS:

Pain and tenderness relieved. Mobility increased. Swellings diminished or disappeared. Muscle strength improved. Rheumatic nodules often disappeared. Even severe or advanced deformity improved. *Active* inflammatory process usually subsided and joint effusion diminished.

GENERAL EFFECTS:

Patients felt and looked better. Exercise tolerance increased. Walking speed and hand grip improved.

LABORATORY EFFECTS:

E. S. R. often fell slowly and hemoglobin level rose gradually.

ANALGESICS AND STEROIDS:

Requirements usually reduced or eliminated.

Dosage: Aralen is cumulative in action and requires four to twelve weeks of administration before therapeutic effects become apparent. The usual adult dose is 250 mg. daily. If side effects appear withdraw Aralen for several days until they subside. Reinstate treatment with 125 mg. daily and, if well tolerated, increase to 250 mg.

If medication is withdrawn, a relapse, if it occurs, will usually be manifest within 3 to 12 months. Resumption of therapy, as above, is generally again effective.

Supplied:

Aralen phosphate: 250 mg. tablets in bottles of 100 and 1000.
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Write for booklet discussing clinical experience, tolerance, precautions, etc., in detail.

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when infection
strikes the respiratory tract . . .

ILOTYCIN

(Erythromycin, Lilly)

provides singularly effective antibiotic therapy because

- Virtually all gram-positive organisms are sensitive
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Dosage: The usual adult dose is 250 mg. every six hours.

Available in specially coated tablets, pediatric suspensions, drops, otic solution, ointments, and I.V. ampoules.

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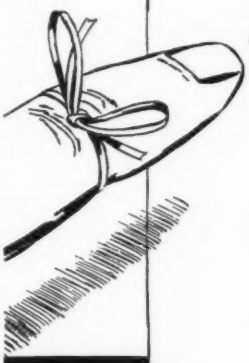

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RIB-BACK

To the Profession it has served with undivided responsibility for so many years . . . BARD-PARKER has devoted its scientific knowledge and the inimitable skill of its craftsmen in developing the finest surgical blade possible . . . a blade that meets the demand of the Profession for quality and economy.

The satisfaction of knowing you have chosen the best is yours when you use B-P RIB-BACK blades.

It's Sharp

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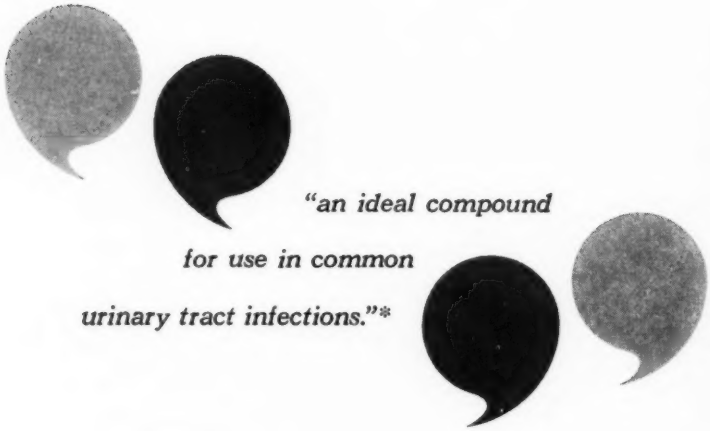
the 'only' RIB-BACK BLADE



Azo Gantrisin provided "prompt and effective clearing of organisms and pyuria"* plus "dramatic relief of bladder and urethral symptoms"* in 221 (97%) of 228 patients with urinary tract infections.

Azo Gantrisin is particularly useful in the treatment of cystitis, urethritis and prostatitis. It is equally valuable following urologic surgery, cystoscopy and catheterization because it provides effective antibacterial action plus prompt pain relief.

AZO GANTRISIN®—500 mg Gantrisin (brand of sulfisoxazole) plus 50 mg phenylazo-diamino-pyridine HCl

*F. K. Garvey and J. M. Lancaster, North Carolina M. J., *18*:78, 1957.

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ORIGINAL RESEARCH IN MEDICINE AND CHEMISTRY

"care of the man rather than merely his stomach"[8]

"Milpath" two-level control of gastrointestinal dysfunction

Miltown® + *anticholinergic*

at the central level The tranquilizer Miltown® reduces anxiety and tension.[1, 3, 6, 7] Unlike the barbiturates, it does not impair mental or physical efficiency.[5, 7]

at the peripheral level The anticholinergic tridihexethyl iodide reduces hypermotility and hypersecretion.

Unlike the belladonna alkaloids, it rarely produces dry mouth or blurred vision.[2, 4]

indications: peptic ulcer, spastic and irritable colon, esophageal spasm, G. I. symptoms of anxiety states.

each "Milpath" tablet contains:

Miltown® (meprobamate WALLACE) ..... 400 mg.
(2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate)

Tridihexethyl iodide ..... 25 mg.
(3-diethylamino-1-cyclohexyl-1-phenyl-1-propanol-ethiodide)

dosage: 1 tablet t.i.d. at mealtime and 2 tablets at bedtime.

available: bottles of 50 scored tablets.

references: 1. Altschul, A. and Billow, B.: The clinical use of meprobamate. (Miltown®). New York J. Med. *57*: 2361, July 15, 1957. 2. Atwater, J. S.: The use of anticholinergic agents in peptic ulcer therapy. J. M. A. Georgia *45*:421, Oct. 1956. 3. Borrus, J. C.: Study of effect of Miltown (2-methyl-2-*n*-propyl-1,3-propanediol dicarbamate) on psychiatric states. J. A. M. A. *157*:1596, April 30, 1955. 4. Cayer, D.: Prolonged anticholinergic therapy of duodenal ulcer. Am. J. Digest. Dis. *1*:301, July 1956. 5. Marquis, D. G., Kelly, E. L., Miller, J. G., Gerard, R. W. and Rapoport, A.: Experimental studies of behavioral effects of meprobamate on normal subjects. Ann. New York Acad. Sc. *67*:701, May 9, 1957. 6. Phillips, R. E.: Use of meprobamate (Miltown®) for the treatment of emotional disorders. Am. Pract. & Digest Treat. *7*:1573, Oct. 1956. 7. Selling, L. S.: A clinical study of Miltown®, a new tranquilizing agent. J. Clin. & Exper. Psychopath. *17*:7, March 1956. 8. Wolf, S. and Wolff, H. G.: Human Gastric Function, Oxford University Press, New York, 1947.

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"A COAT FOR MEPROBAMATE"

CR-622

"Meprotabs" are new, *coated*, white, unmarked 400 mg. tablets of meprobamate. ■ "Meprotabs" are pleasant tasting, and easy to swallow. ■ In this new form, the nature of medication is not identifiable by the patient. ■ "Meprotabs" are indicated for the relief of anxiety, tension and muscle spasm in everyday practice. ■ *Usual dosage:* One or two tablets t.i.d. **"Meprotabs"**

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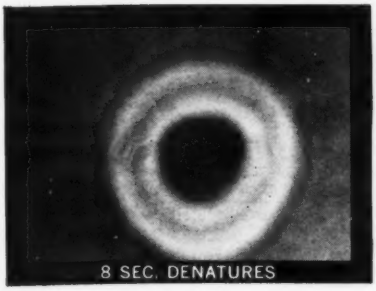
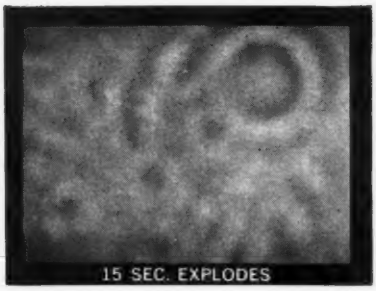
(2-methyl-2-**n**-propyl-1, 3-propanediol dicarbamate)



IN A NEW STUDY of vaginal trichomoniasis in which VAGISEC® liquid and jelly were used, Albert Decker, M.D., reports: "The organism is destroyed by 'explosion' within a few seconds after contacting the [trichomonacide] in a dilution that is nontoxic and nonirritating."[1]

VAGISEC liquid and jelly, used by the Davis technique,† offer a new approach to successful treatment of vaginal trichomoniasis.[1-4] By *exploding* – not merely inactivating – hard-to-reach flagellates as well as those in surface secretions, VAGISEC therapy quickly rids the vagina of trichomonads that tend to survive and cause flare-ups.*

"...destroyed by 'explosion' *within a few seconds...*"



High rate of success – Dr. Decker's new study confirms the effectiveness of these unique agents in both acute and chronic infections. Of 65 women considered to have adequate treatment,* 63 were freed of trichomoniasis. "There was immediate relief of symptoms . . ." and no post-treatment recurrences.

Vaginal infections yield promptly – With VAGISEC liquid and jelly, 58 of the 59 re-infection-free patients showed negative smears after three or four weeks of therapy *and remained negative through three successive menstrual periods* – a criterion of cure. Once extravaginal foci were eliminated, four more cases cleared rapidly. The two failures were in patients whose husbands were infected too.

Explosion unique – Only VAGISEC liquid and jelly explode trichomonads after 15 seconds' contact.[3] A detergent, a chelating agent and a wetting agent, combined in balanced blend, act to weaken the parasites' cell membrane, remove waxes and lipids and denature the protein. Then trichomonads imbibe water, swell and explode. The two surface-acting agents ensure thorough VAGISEC penetration of the vaginal rugae.

Round-the-clock therapy – The Davis technique employs both fast-acting VAGISEC liquid and long-lasting VAGISEC jelly.[3] Physicians use the liquid for office treatments and prescribe it as a home douche, followed by jelly, for 24-hour effective treatment. With this regimen, rate of "cure" averages better than 90 per cent.[4]

Stopping conjugal contagion – To prevent conjugal re-infection, which can and does make the wife's treatment futile,[1-7] many physicians now routinely specify superior RAMSES® prophylactics in writing. These are the ones most men prefer. RAMSES are transparent, smooth, tissue-thin, yet strong, with "built-in" sensitivity. At all pharmacies.

VAGISEC®

LIQUID AND JELLY

Active ingredients in VAGISEC liquid: Polyoxyethylene nonyl phenol, Sodium ethylene diamine tetra-acetate, Sodium dioctyl sulfosuccinate. In addition, VAGISEC jelly contains Boric acid, Alcohol 5% by weight.

REFERENCES:

1. Decker, A.: New York J. Med. *57*:2237 (July 1) 1957.
2. McGoogan, L. S.: J. Michigan M. Soc. *55*:682 (June) 1956.
3. Davis, C. H. (Ed.): Gynecology and Obstetrics (revision), Hagerstown, W. F. Prior, 1955, vol. 3.
4. Davis, C. H.: West. J. Surg. *63*:53 (Feb.) 1955.
5. Draper, J. W.: Internat. Rec. Med. *168*:563 (Sept.) 1955.
6. Karnaky, K. J.: J.A.M.A. *155*:876 (June 26) 1954.
7. Bernstine, J. B., and Rakoff, A. E.: Vaginal Infections, Infestations, and Discharges, New York, The Blakiston Co., 1953.

*For a small percentage of women who have an involvement of cervical, vestibular or urethral glands, additional measures are required.[1,3,4]

JULIUS SCHMID, Inc.

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New York 19, N. Y.

VAGISEC and RAMSES are registered trade-marks of Julius Schmid, Inc.

†Pat. app. for

low back pain

begins to yield in hours

"... is an orally effective and safe antispasmodic drug. Results are prompt, and gratifying to the patient. The number of office visits ... is reduced significantly. The dosage schedule is simple ... side actions are minimal ..." "No toxic side actions were noted."

Finch, J. W.: Orphenadrine (Disipal) in Skeletal Muscle Disorders. To be published.

Dosage: 1 tablet (50 mg.) t.i.d. In Parkinsonism when used in combination with other drugs, smaller dosage may suffice.

In Parkinsonism
Highly selective action... energizing against weakness, fatigue, adynamia and akinesia ... potent against sialorrhea, diaphoresis, oculogyria and blepharospasm ... lessens rigidity and tremor ... mildly euphoriant ... safe... even in glaucoma.

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*Trademark of Brocades-Stheeman & Pharmacia. U.S. Patent No. 2,567,351. Other patents pending.

there are many ways of looking at a cold

from all angles...best for severe colds

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Each CORICIDIN FORTE Capsule provides

CHLOR-TRIMETON® Maleate (chlorprophenpyridamine maleate)	4 mg.
Salicylamide	0.19 Gm.
Phenacetin	0.13 Gm.
Caffeine	0.03 Gm.
Ascorbic acid	0.05 Gm.
Methamphetamine hydrochloride	1.25 mg.

in bottles of 100 and 1000 capsules.

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TABLETS

combining the proved action of CORICIDIN with the added sedative-analgesic action of codeine for more effective relief of the painful symptoms of respiratory disorders—colds, sinusitis, grippe; nonrespiratory conditions—dysmenorrhea, muscular rheumatism, neuralgia

Each CORICIDIN with Codeine◇ Tablet contains	
Codeine phosphate	0.016 Gm. or 0.03 Gm.
CHLOR-TRIMETON® Maleate (chlorprophenpyridamine maleate)	2 mg.
Aspirin	0.23 Gm.
Phenacetin	0.16 Gm.
Caffeine	0.03 Gm.

◇Narcotic for which oral Rx is permitted

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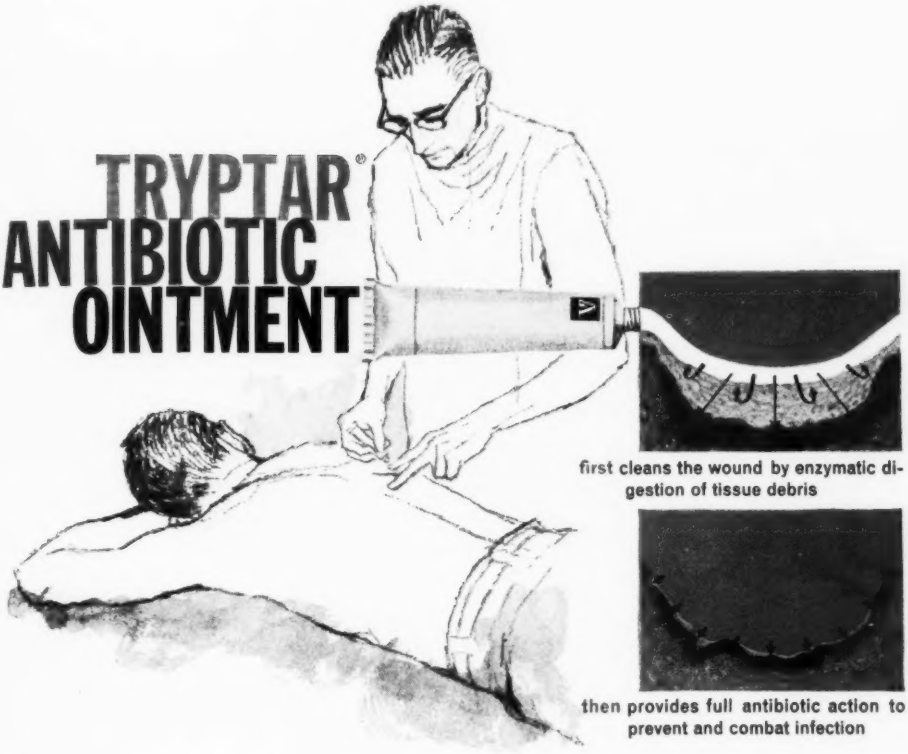
TRYPTAR® ANTIBIOTIC OINTMENT



first cleans the wound by enzymatic digestion of tissue debris

then provides full antibiotic action to prevent and combat infection

Essentially All Wounds Are Dirty

In any breach of skin surface Tryptar Antibiotic Ointment **promotes** and speeds healing... **reduces** inflammation, edema and pain... **overcomes** odors ... **improves** local circulation... **softens** crusts... **helps** produce healthy granulation tissue... and **prevents** edema and infection.

FOR THE FIRST TIME, Tryptar Antibiotic Ointment combines:

2 enzymes	Trypsin Chymotrypsin	for rapid digestion of tissue debris
2 antibiotics	Bacitracin Polymyxin	for rapid healing of cleaned wounds

Safe, virtually nonsensitizing, does not affect living tissue. There are no known contraindications.

Each gram of Tryptar Antibiotic Ointment contains:

Trypsin (crystalline).....5000 Armour Units
Chymotrypsin (crystalline)...5000 Armour Units
Bacitracin U.S.P..... 500 units
Polymyxin B Sulfate U.S.P...5000 units
in a smooth-flowing ointment base of excellent water solubility

Supplied: in ½ oz. and 2 oz. tubes.

THE ARMOUR LABORATORIES
A DIVISION OF ARMOUR AND COMPANY - KANKAKEE, ILLINOIS

When you SEE chronic constipation

...SUSPECT biliary dysfunction

CHRONIC CONSTIPATION MAY SIGNAL A FUNCTIONAL BILIARY STASIS...

especially when accompanied by other symptoms of dyspepsia...with no evidence of an organic problem.

In many instances, the patient will respond effectively to Neocholan therapy which insures free passage of essential bile salts into the duodenum. In such cases relief of constipation and other symptoms is accomplished with gratifying promptness.

NEOCHOLAN®

Each Neocholan tablet supplies:

Dehydrocholic acid	250 mg. (3 3/4 gr.)
Homatropine Methylbromide	1.2 mg. (1/50 gr.)
Phenobarbital	8.0 mg. (1/8 gr.)

Dosage: 1 or 2 tablets t.i.d. with meals. As symptoms improve, 1 or 2 tablets daily.
Bottles of 100 coated, yellow tablets.

PITMAN-MOORE COMPANY
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NEW . . . intranasal synergism

℞

Biosynephrine™

Nasal Spray

15 cc.

Contains:

DECONGESTIVE
Neo-Synephrine® HCl 0.5%

ANTI-INFLAMMATORY
Hydrocortisone 0.02%

ANTI-ALLERGIC
Thenfadil® HCl 0.05%

ANTIBACTERIAL
Neomycin (sulfate) 1 mg./cc.
(equivalent to 0.6 mg. neomycin base/cc.)
Polymyxin B (as sulfate) 3000 u/cc.

Convenient plastic, unbreakable squeeze bottle. Leakproof, delivers a fine mist.

POTENTIATED ACTION for better clinical results

in COLDS
SINUSITIS
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Neo-Synephrine (brand of phenylephrine) and Thenfadil (brand of thenyldiamine), trademarks reg. U.S. Pat. Off.

INTRAVENOUS Compatible with common IV fluids. Stable for 24 hours in solution at room temperature. Average IV dose is 500 mg. given at 12 hour intervals. Vials of 100 mg., 250 mg., 500 mg.

THERAPEUTIC BLOOD LEVELS ACHIEVED

Many physicians advantageously use the parenteral forms of ACHROMYCIN in establishing immediate, effective antibiotic concentrations. With ACHROMYCIN you can expect prompt

NTRAMUSCULAR Used to start a pa-
ient on his regimen immediately,
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ontrol, with minimal side effects,
ver a wide variety of infections -
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during and after surgery

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A COMPLETE SYSTEMIC HEMOSTAT

Adrestat complements the surgeon's skill by providing a new concept in the control of operative and postoperative bleeding. It promotes retraction of severed capillary ends and controls capillary bleeding and oozing; prevents bleeding due to hypoprothrombinemia; and prevents or corrects abnormal capillary permeability and fragility. Indicated in virtually every surgical procedure and in hypoprothrombinemia.

AVAILABLE:

ADRESTAT *capsules and lozenges, each containing:*

Adrenochrome Semicarbazone (present as Carbazochrome Salicylate, 65.0 mg)*	*2.5 mg*
Sodium Menadiol Diphosphate (Vitamin K Analogue)	*5.0 mg*
Hesperidin, Purified	*50.0 mg*
Ascorbic Acid	*100.0 mg*

Capsules in boxes of 30; Lozenges in boxes of 20

ADRESTAT (F) — *1-cc ampuls, each containing:*
5 mg Adrenochrome Semicarbazone (present as Carbazochrome Salicylate, 130.0 mg)*
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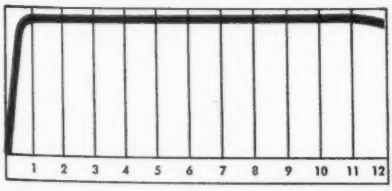

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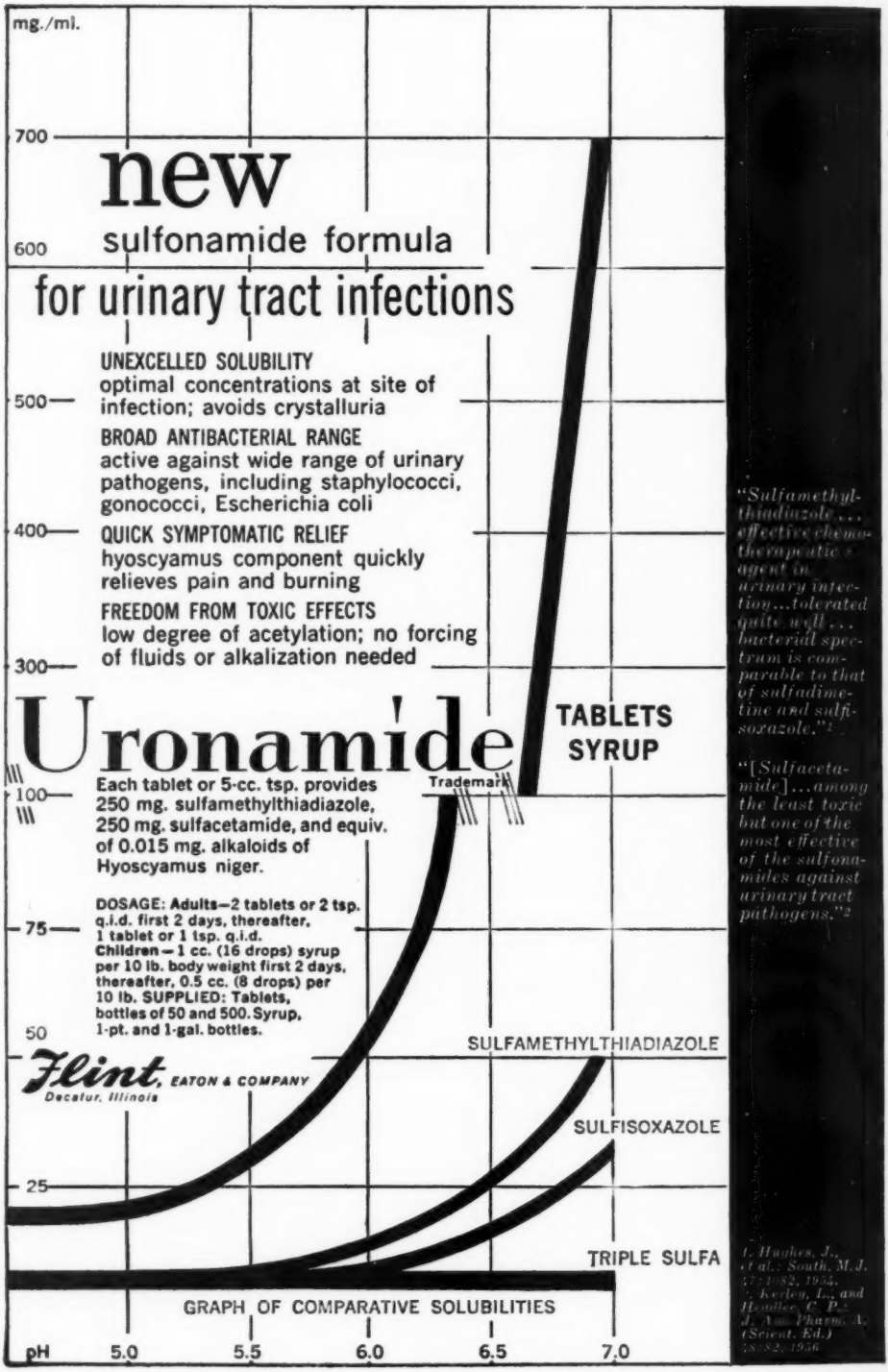
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2. Kerley, L., and Hoeller, C. P.: J. Am. Pharm. A. (Scient. Ed.) 38:82, 1956

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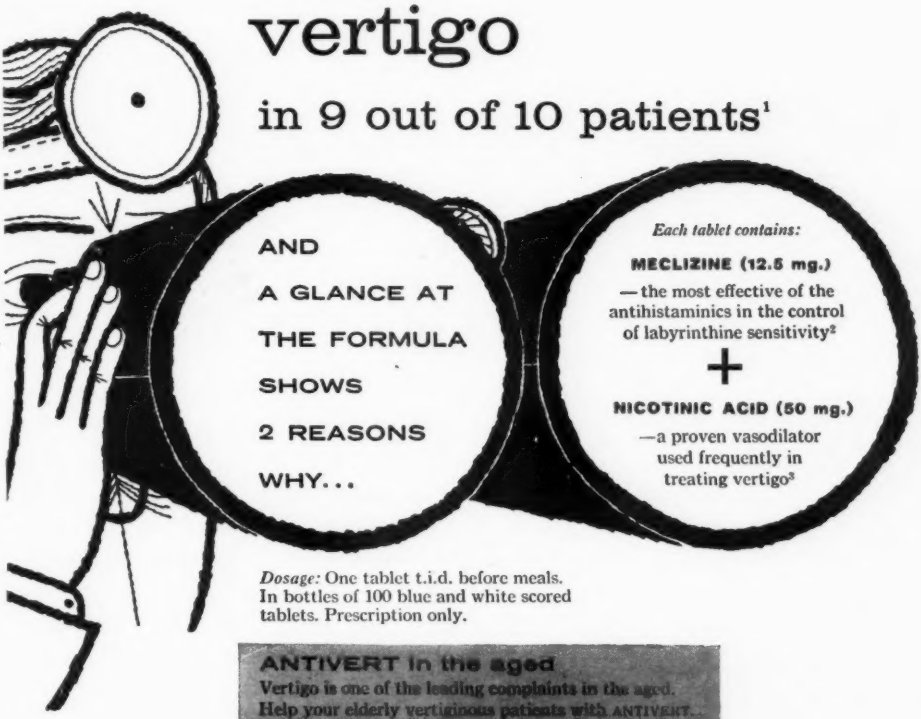

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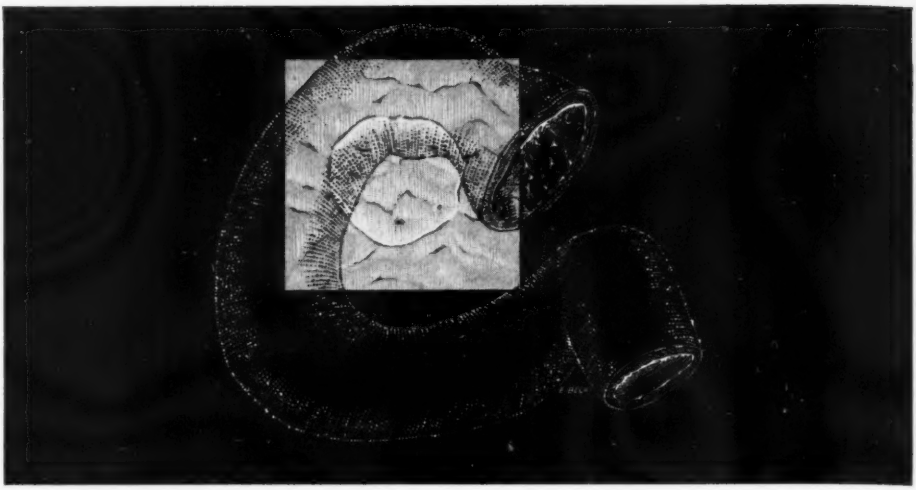

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1. Jones, Georgeanna S. and Smith, Frank: Am. J. Obstet. Gynecol., Vol. 67: No. 3, 628-633, 1954.
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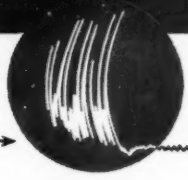

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Southern Medical Journal

PUBLISHED BY SOUTHERN MEDICAL ASSOCIATION

December 1957

The Coexistence of Diverticular Disease and Adenomatous Polyps of the Colon*

A. F. CASTRO, M.D.,† *Washington, D. C.*

Attention is directed to the combination of colonic polyps and diverticula, pointing up difficulties in diagnosis and the influence on the choice of treatment.

IN THE STUDY of a disease many aspects are to be considered if we are to arrive at a satisfactory and complete understanding of the entire problem. The study of the association of two diseases will, in certain cases, throw light on the understanding of one, if not both of them.

This work was begun about one year ago, prompted by two observations: (1) the difficulty encountered in accurately diagnosing adenomatous polyps in areas of diverticular disease; and (2) the possibility that the number of patients with adenomatous polyps was greater in that group also having diverticulosis.

The correct incidence of diverticulosis in the general population is a difficult figure to assess. Many articles dealing with such statistics have been written, and current opinion has it that about 5 per cent of individuals over the age of 40 have diverticulosis. We also know that involvement of the sigmoid colon occurs in 80 per cent of these cases.

Likewise, the incidence of adenomatous polyps in the colon or rectum has been the subject of numerous publications. Here, however, agreement has been less universal. Reported figures on the incidence of these tumors vary between 2 and 15 per cent.

One outstanding fact in all of these studies is that the older the individual, the greater the likelihood of developing both diverticulosis and adenomas in the colon. These conditions are degenerative diseases of the colon, and it stands to reason that an increase in their occurrence should be expected as the colon begins to wear out.

It would seem far fetched to think of adenomas as predisposing a patient to diverticulosis,—but what of the contrary? We know that chronic irritation can be a factor in neoplasia. We also know that a colon subject to diverticular disease frequently shows spasticity and inflammatory changes in its wall, therefore increasing the irritant factors present. Proof, one way or the other, is difficult to obtain and, as yet, this type of study is in its infancy. Review of the literature failed to elicit any contribution in which the association of these two diseases is considered.

Diagnosis

This work represents facts obtained from 110 consecutive patients having diverticulosis or diverticulitis. They showed a definite rise in the incidence of adenomatous polyps if

TABLE 1

DIVERTICULAR DISEASE OF THE COLON (110 CASES)

Patients with coexisting adenomatous polyps:	
In colon or rectum	25 (22.7%)
Those in area of diverticular disease	14 (12.7%)
(a) In area of diverticulosis	9 (8.2%)
(b) In area of diverticulitis	5 (4.5%)

*Read before the Section on Proctology, Southern Medical Association, Fiftieth Annual Meeting, Washington, D. C., November 12-15, 1956.

†From the Proctology Clinic of Washington, Washington, D. C.

compared with the over-all percentage scales (Table 1). We must consider though, that the average age of this group of patients was 60, and by that time the incidence of adenomatous polyps has increased even in the absence of diverticulosis. Statistics again are lacking; suffice it to say that further study will be necessary along these lines to arrive at a definite conclusion.

The diagnosis of adenomatous polyps in the presence of diverticular disease is the principal point of this writing. We are all cognizant of the danger of malignant degeneration if adenomatous polyps are not removed from the bowel. Therefore, any condition that increases the difficulty of detecting these growths in the colon should be looked upon as a stimulus for more careful evaluation of the diagnostic procedures used and of the findings obtained with them.

In the presence of diverticulosis, and particularly in diverticulitis, the difficulty in diagnosing intraluminal bowel tumors is directly proportional to the amount of involvement of the colon by the diverticular disease. Difficulties are particularly encountered during endoscopic procedures, or at the time of barium enema. The value of proctosigmoidoscopy in diagnosing diverticulosis has been well established. The diverticular openings are fairly easily recognized. When inflammatory changes plus scarring and thickening of the bowel wall occur, as in the case of diverticulitis, the lumen of the bowel is narrowed in direct proportion to the degree of involvement present.

As the disease progresses shortening and angulation of the sigmoid and rectosigmoid begin to occur. This decrease in the size of the bowel lumen, plus the ensuing angulation make proctosigmoidoscopy extremely difficult, if not impossible. Yet, it is in these cases, as well as in the case of any other disease of the colon causing similar changes, that visualization of the colonic mucosa is of greatest importance. The fact remains that the more difficult the procedure, the greater the knowledge obtained by perseverance in its performance. The use of small caliber scopes is definitely recommended in these difficult cases, but one must be judicious in their use since the possibility of rupturing a friable bowel is ever present. Sigmoidoscopic visualization of the colonic mucosa of an area of diverticulosis or diverticulitis certainly will rule out adenomatous polyps in cases where a barium enema study wrongly suggests their presence.

The difficulties found in discovering adenomatous polyps in the colon by barium enema are well known to the roentgenologist. These difficulties increase inversely proportional to the size of the polyp. A polypoid tumor measuring less than 0.5 cm. in diameter may be missed in a barium enema, whether or not the rest of the colon is normal. If inflammatory changes are present in the bowel wall, detection of these tumors is made more difficult or, in some cases, impossible. Perhaps equally important is the finding of small defects in the barium column, or in the mucosal pattern of barium in diverticu-

FIG. 1

Diverticulosis of the colon with a barium shadow simulating an adenoma.

FIG. 2

In this view the previous shadow is seen to be formed by a diverticulum which is almost empty of barium at this exposure.

losis and/or diverticulitis, suggesting the presence of adenomatous polyps.

A second barium enema is definitely indicated in these cases, and more accurate studies can be carried out if one waits several weeks before repeating the barium study. During this interval treatment of the diverticulitis will aid in the solution of this problem.

Finding the same defect in the same location would favor the presence of an adenomatous polyp. In some cases, however, one must differentiate between a polypoid tumor and a barium filled diverticulum that is viewed "head on" (Figs. 1 and 2). A lateral view of the colon, which incidently is not frequently done, can definitely aid in distinguishing one from the other.

Barium enemas and sigmoidoscopic examinations were done in the 110 cases under consideration. As stated before, adenomatous polyps were found in 25 patients. Eleven of these presented the polypoid tumors in the rectum and away from the area of diverticular disease. A comparison of the successful diagnostic procedures used in the 14 remaining cases, (those with adenomatous polyps in an area of diverticular disease of the sigmoid colon), is shown in table 2.

TABLE 2

8 were diagnosed by proctosigmoidoscopy alone.
3 were diagnosed by both proctosigmoidoscopy and barium enema.
2 were diagnosed by barium enema alone.
1 was diagnosed only in the resected specimen.

Unsuspected adenomatous polyps are not a rarity in surgical specimens of the colon, regardless of the reason for the surgical procedure. One of our cases belongs to this group. Two barium enemas and several proctosigmoidoscopic examinations, which could be carried only to 18 cm., failed to demonstrate the growth, even though it measured 2 cm. in diameter. It was located in the midsigmoid in an area of active diverticulitis. Of the 5 cases diagnosed by barium enema, 3 were also reached by sigmoidoscopy. In another of these cases, two barium enema studies showed the tumor very plainly, but visualization of the polyp by sigmoidoscopy was impossible until a third attempt was made while

FIG. 3

The adenomatous polyp is shown on the film. Mild diverticulitis is also present. The tumor was easily visualized by sigmoidoscopy.

the patient was under chemotherapy in preparation for laparotomy. Therefore this patient required only a local excision of the polyp by snare and electrocoagulation of the remaining base, instead of laparotomy (Fig. 3). Two cases were diagnosed by barium enema only; the polyps were too high to be seen on sigmoidoscopy and laparotomy was necessary.

The eight tumors diagnosed by endoscopy alone varied from 3 mm. to 1.5 cm. in diameter. It is in these cases that diagnosis may not be established if sigmoidoscopy is incomplete. It is true that 5 of the 8 were small, but 3 of these lesions measured between 0.5 and 1.5 cm. in diameter, and yet were not discovered in the barium study.

Bleeding does occur in cases of diverticulosis and/or diverticulitis. It may also arise from polypoid tumors of the colon. Therefore it stands to reason that one must redouble the efforts to rule out the presence of a polypoid tumor in diverticulitis with bleeding. Repeated barium enema and sigmoidoscopic examinations are weapons upon which we can rely to adequately follow the course of a case of this sort.

These observations point out the difficulties encountered in the diagnosis of these combined lesions and the importance of a more thorough and careful study of an area of diverticulitis to exclude the presence of coexisting adenomatous polyps. Not only one, but several endoscopic and barium studies should be made in these patients at different intervals. This is particularly true whenever medical treatment is chosen as the best approach to the management of a particular patient.

Treatment

The treatment of these patients varies. It may be quite easy, as in the majority, where a small adenoma is amenable to local eradication by electrosurgery. It may be technically more difficult, as in the case where a length of bowel is resected for diverticulitis and the polypoid tumor is removed with it. Or, it may be subject to much speculation and worry if medical treatment is preferred for diverticulitis, but suspicion of the presence of a small polypoid tumor is suggested either by a barium enema or by blood being noticed in the stool of that patient.

The modern trend in the treatment of diverticulitis favors earlier resections instead of waiting until abscess, fistula, or obstruction has occurred. Of course, every case must be individually evaluated and we cannot arrive at the proper method of treatment until all points have been considered. All things being equal, the presence of an adenomatous polyp in areas of diverticulitis is an added incentive for the early segmental resection of the involved bowel.

Conclusion

This review was undertaken mainly to bring out the difficulties and importance of diagnosing adenomatous polyps in the presence of diverticulosis and/or diverticulitis.

The apparent increase in the percentage of patients having adenomatous polyps when diverticular disease is also present can be easily explained by an increase in the later age group of these people, and by the fact that these patients came in with symptoms of colonic trouble, rather than belonging to the usually quoted asymptomatic group.

Management of the Later Stages of Chronic Pulmonary Emphysema*

WYNDHAM B. BLANTON, JR., M.D., and
JOHN L. PATTERSON, JR., M.D.,† *Richmond, Va.*

The proper regimen selected for the management of the individual patient suffering from the late stages of chronic pulmonary emphysema is most essential for his comfort and the continuation of a happy and productive existence.

THE MANAGEMENT of the late stage of chronic obstructive pulmonary emphysema constitutes an increasing problem to the physician of today. Increased longevity in the population, together with improved, but still only partial control of chronic bronchitis and asthma, which represent precursors of chronic pulmonary emphysema, has permitted more patients to move into the later stages of this condition. An understanding of the relentless and largely nonregressing character of the pathologic changes of advanced obstructive emphysema clearly shows that a "cure" of the condition is impossible. This combination of an increasing incidence and irreversibility emphasizes the need for a prophylactic approach in the control of the disease, and stresses the importance of continued improvement in technics of management.

In the discussion which follows the major weapons in the management of advanced stages of chronic pulmonary emphysema are considered. Particular emphasis is placed on certain aspects of management which, in our opinion, are insufficiently stressed.

Bronchodilator Agents

These are an essential component in the treatment of pulmonary emphysema, but it is not our intention to compare such drugs beyond stating that isopropylaretenol (Isuprel) has been the most useful in our experience.

Each of the available routes of administration of the different agents, oral, sublingual, rectal, and parenteral is useful. For example, the oral administration of such bronchodilators as ephedrine or theophylline derivatives, is of value not only early in the disease but also in late emphysema as mild "background" bronchodilator therapy. Bronchospastic crises, however, demand an aerosol or parenteral route. Aminophylline by intravenous drip, and occasionally, meperidine (Demerol) intramuscularly may be used cautiously in severe bronchospastic crises.

The frequency of dosage must often be increased far beyond what is usually considered adequate. In difficult situations the majority of patients can tolerate isopropylaretenol (Isuprel) 0.5 cc. in a dilution of 1:200 every two hours, and even as often as every hour. Some patients, because of palpitation or other symptoms, must be held to less frequent usage, more dilute solutions, or smaller dosage.

Technic can mean the difference between success and failure in aerosol therapy. The exhausting effect in an already tired patient of having to use a hand nebulizer can be overcome by utilizing a supply of oxygen or compressed air with a "Y-tube" to create a supply on demand. Instead of closing his lips about the nebulizer, the patient should leave a crack at either side of the mouth beside the tube. In this way the aerosol is swept into the trachea with a large incoming flow of air, rather than being largely lost in the saliva. Intelligent patients will obtain the maximum effect from a given volume of bronchodilator by learning to interrupt the flow of aerosol just prior to the end of inspiration so that the material is actually carried through much of the dead space, with very little being lost in the next expired breath. Some of the intermittent positive pressure breathing (IPPB) devices provide excel-

*Read before the Section on Medicine, Southern Medical Association, Fiftieth Annual Meeting, Washington, D. C., November 12-15, 1956.

†From the Department of Medicine, Medical College of Virginia, Richmond, Va.

lent bronchodilator effects through aerosols. A number of patients, particularly those with tracheobronchial exudates which are difficult to raise, obtain more relief from an aerosol plus IPPB than from aerosol alone. Immediately after such treatment there is often an increase in the production of sputum.

One should not leave the subject of bronchodilators without noting the inconsistency, too often seen, of prescribing these agents without at the same time insisting on the patient's avoidance of bronchial irritants which can produce increased resistance in the airway, tobacco, in particular, but also fumes including those from the strong floor cleansing agents, house dust and others important in specific cases.

Antibiotics

Control of infection is often the key to successful management in the late stage of emphysema. In many patients continuous or intermittent maintenance of antibiotic therapy is necessary. Too frequently, if one waits for obvious evidences of an acute exacerbation, the disease process has progressed undesirably far by the time the acute change is recognized. These chronically ill, frequently debilitated, and often elderly people may show minimal to no evidence of infection, when judged by the usual signs of fever, leukocytosis, and increase in pulse rate. Increase in cough, with or without a change in volume or character of sputum, and a decline in the sense of well-being are usually the earliest manifestations of an exacerbation of infection.

In maintaining antibiotic therapy, to obtain adequate results within the limits of tolerance of the host and to minimize the development of bacterial resistance, it is our practice to employ an empirical but individually designed schedule of rotation through two or more antibiotics in moderate dosage, in contrast to the constant small dosage of one agent as advocated by some. Such a schedule may vary with the season of the year, since in the warmer months the interval between periods of administration of the antibiotics can frequently be lengthened. Tetracycline, chloramphenicol, penicillin-V and erythromycin by mouth, and penicillin, or rarely penicillin and streptomycin intramuscularly comprise the most useful armamentarium of maintenance therapy.

In our opinion, the disadvantages of antibiotic aerosols outweigh their advantages and we rarely use them.

Diaphragmatic Control

An individualized plan of instruction in the voluntary control of the diaphragm is sometimes helpful. Such management is most effective if started early in the course of the disease, when the patient is able to tolerate alterations in his pattern of breathing and has time to develop the habit which will enable him to continue such control when faced with an acute exacerbation of respiratory difficulty. The breathing instructions should be based on the findings at fluoroscopy and of ventilatory function tests. In general, it is our feeling that such instruction should be directed toward increased effectiveness of the *expiratory* phase of the respiratory cycle through contraction of the abdominal muscles. There are a few patients, however, apparently unduly fatigued by this method, or having somewhat higher diaphragms or less of a barrel chest who benefit by emphasis on active *inspiration*.

It is in those patients who, for various reasons, are unable to elevate their diaphragms on expiration that the so-called emphysema belts may have some beneficial effect. We feel reasonably certain that to be most effective such belts should be specifically designed with regard to the particular patient's anatomic configuration, be placed low on the abdomen, and be made for use with all types of clothing. In our area it is impossible to get an adequate belt individually fabricated. Therefore we have used a stock belt on a trial basis; if it is ineffective or objectionable to the patient the idea of such help must be abandoned.

Management of Emotional Aspects

For some time we have been impressed with the rather characteristic personality of the patient in the late stage of emphysema. Almost without exception he is introverted, demanding, capable of tremendous attachments of dependency, opposed to changes in the therapeutic regimen, intolerant, impatient, frightened of gadgets, and unwilling to submit to adequate therapeutic trials. Certainly this is not a surprising reaction in the face of this terrifying disease with its insistent

breathlessness of which the patient is rarely unconscious and which to him represents an ever-present threat to survival. This is mentioned because it constitutes a very real factor to be reckoned with in therapy, rather than just tolerated. The physician's success will be poor in handling the patient with severe emphysema if he does not have the time, patience, and perseverance to sit down with him to encourage, demonstrate, cajole, urge, and explain and re-explain a multitude of seemingly inconsequential problems. He must also act as pacifier and interpreter between numerous personalities who may be irritated by the patient and who may turn away from him if not tactfully handled.

Great care must be taken to see that the patient's dependency is directed toward persons who can be of therapeutic benefit to him, that changes in treatment are effected only when necessary and then thoroughly and enthusiastically presented, that efforts are made toward providing some source of emotional satisfaction, and that the patient is permitted to become a physical invalid no more rapidly than is absolutely necessary. Mild physical activity, if possible useful activity, should be encouraged.

Sedatives in mild doses to aid in nocturnal sleep may be indicated, but one must recognize that the tension and anxiety contributed to by the hypoxia of late emphysema responds poorly and often in paradoxical fashion to a barbiturate and other sedatives. Early trials would indicate that chlorpromazine and meprobamate have a place in the management of these patients.

Use of Steroids

These substances represent an important advance in the management of advanced chronic pulmonary emphysema. The advent of prednisone and prednisolone, with their lower tendency to produce sodium retention, has made steroid therapy practical over extensive periods of time. The technic of their use is similar to that in other long-term situations, with careful observation to detect early manifestations of the complications of steroid therapy. These include exacerbation of pulmonary tuberculosis and other infections, or of peptic ulcer, and the production of osteoporosis and serious adrenal atrophy. A maintenance dosage of 15 to 20 mg. per day of prednisone or prednisolone is usually sufficient.

It is our present feeling that such therapy should be reserved for late emphysema because of the complications, but we foresee the possibility that future work may demonstrate that steroids have a real use early in the disease in preventing progression of emphysema.

Use of Oxygen

The dangers inherent in the inhalation of oxygen by patients with arterial hypoxia and high blood levels of carbon dioxide limit its use in late pulmonary emphysema to periods of acute respiratory difficulty, except when mechanical respiratory aids are used simultaneously. During such emergencies, although it seems strange that an apparently trivial amount of oxygen may be of benefit, we have seen it repeatedly demonstrated that oxygen by nasal catheter at a rate of 1 to 2 liters per minute can provide definite reduction of dyspnea and alleviation of anxiety. When oxygen is used in this way coma is uncommon, but milder degrees of carbon dioxide narcosis are quite frequent. Careful observation must be carried out to "titrate" the patient with oxygen to the point where there occurs an increase in the oxygen saturation of the blood and tissues, but where the concurrent rise in arterial carbon dioxide is below a harmfully narcotic level.

In addition to the relief of dyspnea and anxiety associated with arterial hypoxia, this technic is frequently a necessary part of the treatment of cor pulmonale and congestive failure in the patient with emphysema. Digitalis is relatively ineffective in such patients unless the hypoxia is reduced.

A brief period, 20 to 30 minutes, of oxygen administration immediately before meals may enable the patient to eat a larger meal by reducing dyspnea. When intensive or prolonged oxygen therapy is required in late pulmonary emphysema, it is imperative that some type of mechanical assistance to respiration be supplied to prevent reduction in alveolar ventilation.

Mechanical Aids to Respiration

Mechanical respirators, in our work chiefly the Drinker, have several uses in advanced pulmonary emphysema. In the crises produced by acute pulmonary infection the temporary

use of the respirator in conjunction with control measures for infection is of irreplaceable benefit in some patients. Carbon dioxide coma likewise demands a respirator or automatic cycling valves providing intermittent positive inspiratory pressure with or without negative pressure on expiration.

There is insufficient appreciation of the rapidity with which a circular mechanism can produce deterioration of the patient's condition and death. The increasing weakness which characterizes the late stages of this disease leads to an associated diminution in respiratory effort which in turn produces increasing hypoxia and hypercapnia, this then contributing to further weakness and reduction in pulmonary ventilation and so on in a self-accelerating cycle. In addition to hypoxia inadequate nutrition contributes to the weakness. Anorexia is common, even with attractive meals, and even when these patients do have an appetite, the urgency to breathe may prevent adequate time for chewing and swallowing. With the use of a mechanical respirator and oxygen at full rates of flow, it is surprising how rapidly improvement in most of these patients occurs. Discontinuance of the respirator may be possible after several hours, and usually is possible within 1 to 3 days, often leaving the patient in an improved and relatively stable state for weeks or months, occasionally for a year or more. A considerably longer period in the respirator, e.g., 1 to 3 weeks, may be required if the patient is being carried through an acute pulmonary infection.

Finally, we have become increasingly aware of a more controversial use of the respirator in late emphysema, i.e., in patients who will probably be dependent upon its help for all or a part of each day for the remainder of their lives, and who, with such aid, might continue to live for months and perhaps years. The decision concerning such a use raises ethical, moral, social and economic questions. The answer to this dilemma is not clear, but at present we are swayed by the fact that experience has demonstrated that an occasional patient will survive a seemingly moribund crisis to go on with a relatively tolerable life for an indeterminate period again. Such therapy should never be instituted without the full awareness of both physician and family as to the possible course of events.

With regard to the detailed management of patients in the Drinker respirator, we shall only stress two points: (1) most of these patients will require a higher negative pressure to produce adequate inspiration than does the patient with a more nearly normal caliber of the airway, such as the patient with poliomyelitis and respiratory paralysis; and (2) a tracheotomy is frequently necessary so that adequate control of secretions by catheter suction is possible.

Other mechanical aids to breathing are undoubtedly of benefit in the treatment of emphysema in acute situations. However, our own experience with the prolonged use of intermittent positive pressure breathing devices, as the Bennett valve, has been rather disappointing, because patients become fatigued after using these machines for a period of hours. This places definite limits on their use.

Ablation of the Thyroid

The final therapeutic procedure to be discussed, that of ablation of the thyroid gland, is employed at present as a last resort in the management of late emphysema. The theory is simple. Since oxygen available for transport to the tissues cannot be increased beyond an insufficient maximum in late emphysema, tissue demand can be brought into line with oxygen supply through the creation of a hypometabolic state by the action of radioactive iodine on the thyroid gland.

The cases which have been reported, in which this procedure was utilized, suggest that moderate optimism is warranted. The majority of patients have shown an increase in arterial oxygen saturation, diminution in dyspnea, and an improvement in the sense of well-being. The results in 5 patients treated at the Medical College of Virginia have been equivocal. A number of circumstances complicate and detract from this technic. Since a myxedematous state is produced, including an annoying lethargy in some patients, its use must be approached with considerable thought and it is probably wise to delay it as long as possible. Decision to use the procedure must, however, be made far in advance of the moment of urgent need, because it usually requires a total of 4 to 6 months to obtain maximal results. Several months of delay in the institution of the procedure may be necessary if iodides have been used recently in

treating the patient, unless use is made of the administration and withdrawal of antithyroid drugs or of the expensive thyroid-stimulating hormone.

Clinical evaluation of the results of radioactive iodine therapy in this disease is extremely difficult because of its normal fluctuating course. Considerably more objective data will be necessary in order to draw final conclusions as to the benefits of the procedure.

Pulmonary Function Studies

A few pulmonary function tests play a necessary part in the management of the late-stage of pulmonary emphysema. They provide the objective data helpful in evaluating the patient's dyspnea and in properly timing therapeutic procedures. Exhaustive studies are not required and may actually be harmful. Comparison of slow and fast vital capacities affords an indication of the amount of air trapped, and obstruction to the airway may be estimated by the amount of air expelled during the first, second, and third seconds of forced expiration or, somewhat more effectively, perhaps, by these measurements plus study of the shape of the forced expiratory curve. Although the maximum breathing capacity is still quite useful, it has the disadvantage of tiring the patient and producing trapping of air with an increase in dyspnea. It is actually misleading on occasions. Fluoroscopy is essential to the adequate evaluation of a maximum breathing capacity. Oxygen saturation is perhaps the most helpful blood gas study, but unfortunately the lack of a simple determination hampers its usefulness. Determination of plasma or serum carbon dioxide by titration of the bicarbonate is a simple procedure and, even when carried out on venous blood, is quite helpful in the detection of variations in the degree of carbon dioxide retention.

We are cognizant of the developments in surgery of the autonomic system applied to the management of these patients, and have asked Dr. Abbott to comment on these in his discussion.

Summary

The late stage of pulmonary emphysema is a disease which will be managed adequately only if there is an individual adaptation of treatment to each specific patient's need. The principle weapons in the management of the disease are bronchodilator agents, antibiotics, instructions in breathing, management of emotional aspects, steroid drugs, carefully controlled use of oxygen, mechanical aids to respiration, and possibly thyroid ablation. A few properly chosen pulmonary function tests are helpful.

Acknowledgment

The authors wish to express appreciation to Dr. Richard H. Kirkland of the Department of Medicine, Medical College of Virginia, who carried out the radioactive iodine studies and treatment on the patients, and to Miss Edith Hardie, Technician of the Pulmonary Function Laboratory.

Discussion (Abstract)

Dr. Osler A. Abbott, Atlanta, Ga. Drs. Blanton and Patterson have completely and clearly outlined the basic problems in the later stages of chronic pulmonary emphysema. It is my purpose to mention briefly the role which surgery may play in this stage of the disease. Table 1 outlines the procedures which may be involved.

We make a practice of utilizing bronchoscopy in almost all patients with this disease. The rationale is to clean out tenacious or purulent secretions. The bronchoscope has a very strong and effective action as an expectorant. The irritant effect of passing the instrument, the use of topical shrinking agents upon the bronchial mucosa, subsequent saline irrigation, and the cough occurring attendant to the procedure all aid in getting air into previously nonfunctioning alveoli. This improves alveolar ventilation. The response of the patient to the procedure, especially in regard to the volume and character of the bronchial secretions provided in the immediate 24 hours after endoscopy, define the need for repetition of the operation in from 3 to 5 days. Bronchoscopy is a distinct aid in controlling the suppurative tracheobronchitis so frequently attendant to the later stages of chronic pulmonary emphysema. Special precautions are required to prevent hazardous degrees of laryngobronchospasticity being produced by the maneuver.

The surgical excision of pulmonary tissue is of occasional use in highly selected cases. Fundamentally it is to be considered if x-ray and fluoroscopic studies reveal a significant local character to the disease. One would require evidence that a localized area of more

TABLE 1

SURGERY FOR HYPERTROPHIC EMPHYSEMA

I.	Bronchoscopy
	a. Diagnostic
	b. Therapeutic
II.	Excisional surgery
	a. Bullae
	b. Localized major foci
	1. Compressive factor
	2. Trigger mechanism
III.	Pulmonary vagotomy
IV.	Excisional surgery plus vagotomy

advanced disease, such as a severely distended upper lobe with little or no discernible pattern of finer vasculature remaining, was significantly compressing and making less functional potentially useful adjacent pulmonary tissue. Large emphysematous bullae may be present in the mixed bullous and hypertrophic type of emphysema and act in this manner. Or, a case of pure hypertrophic emphysema may present the major localization of the disease in one lobe or group of pulmonary segments. Surgery of this type is generally accepted throughout the medical world. In our clinic we would combine such an operative procedure with complete unilateral pulmonary vagotomy.

Let me briefly mention the background for vagotomy in this disease. Table 2 represents the known action of the vagus nerve as derived from our studies of this disease since 1945.

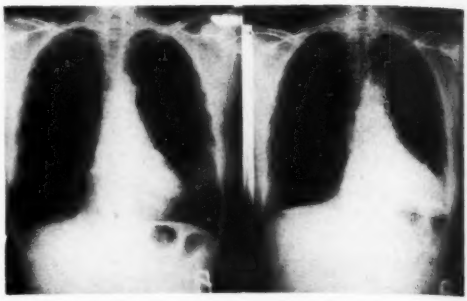
Prior to the advent of significant sclerosis of the pulmonary arterial bed, which is secondary to prolonged chronic pulmonary emphysema, pharmaceutical or direct block of the vagus nerve in emphysema patients reduces pulmonary artery pressure if elevated at rest. Furthermore, it suppresses in varying degree the rise in pulmonary artery pressure seen in response to exercise in this disease. Ventilatory studies have shown that maximum breathing capacity and oxygen uptake are significantly increased by the intravenous injection of vagus nerve blocking agents. In corresponding fashion, studies of femoral arterial blood will show a decrease in carbon dioxide content and an increase in the oxygen saturation in response to such drugs. Finally, at the operating table we have demonstrated an increase in the oxygen content and a decrease in the carbon dioxide content of pulmonary venous blood resultant to direct Novocaine block or transection of the vagus nerve components going to the lung. Early results of studies now in progress show that block of the sympathetic nerve fibers to the normal lung produce an increase in pulmonary artery pressure. In one instance, in a patient with hypertrophic emphysema, isolated block of the sympathetic nervous system so increased the degree of bronchospasm as to require immediate block of the vagus nerve. We are not yet able to report the effects of sympathetic or parasympathetic nerve block upon pulmonary blood flow. Clinically, we have been pleased with the response of patients with hypertrophic emphysema to complete unilateral or bilateral vagotomy. Their response has remained satisfactory even after several years of observation. More recently we have gone so far as to operate upon several patients with actual cor pulmonale. In the majority of such cases the results have been indeed gratifying. Successful extrapleural pulmonary vagotomy has been repeatedly accomplished in patients whose maximum breathing capacity has fallen into the 15 to 20 liter per minute range.

TABLE 2

ACTION OF VAGUS NERVE IN EMPHYSEMA

1.	Elevates pulmonary artery pressure at rest.
2.	Allows rise pulmonary artery pressure on exercise.
3.	Decreases maximum breathing capacity.
4.	Decreases oxygen uptake.
5.	Promotes increase residual air.
6.	Decreases arterial oxygen saturation.
7.	Increases arterial carbon dioxide content.
8.	Decreases pulmonary ventilation oxygen content.
9.	Increases pulmonary ventilation carbon dioxide content.
10.	Effect pulmonary artery flow.

FIG. 1



Inspiration-expiration roentgenographic study in a patient with severe hypertrophic type of pulmonary emphysema. The more advanced character of the disease on the right side can be demonstrated in this manner, but more adequately by careful fluoroscopy.

Finally, I would like to present one film (Fig. 1) demonstrating the importance of fluoroscopic investigation of these patients. As shown here there is a significant shift of the heart and mediastinum to the left on full expiration. This plus the difference in activity and contour of the right and left diaphragms reveal that there is significantly greater obstruction to expiration in the diffusely emphysematous right lung. Bronchoscopy revealed no localized endobronchial obstructing lesion. Complete pulmonary vagotomy on the right dramatically and significantly improved the ventilating and respiratory capacity of this patient. This tendency to localized major intensity of the disease in patients with hypertrophic emphysema is not rare and must always be investigated.

In summary, let me again compliment Drs. Blanton and Patterson. They have summarized well the medical methods useful for the later stages of this disease. If surgery is resorted to, such measures must be assiduously applied in the preoperative and immediate postoperative periods. I have tried to present briefly the rationale for the role which surgery can play in the therapeutic program. Also, attention has been drawn to the unilateral preponderance of the disease which may occur in a patient with pure hypertrophic type of pulmonary emphysema.

Emergency Definitive One-Stage Surgery for Intestinal Obstruction*†

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The authors illustrate that a one-stage operation under emergency conditions is a safe procedure for an acutely obstructed intestine, whether of the small or of the large bowel.

IN 1954 WE[1,2] BEGAN TO TREAT acute intestinal obstruction by one-stage definitive surgery. Our method of approach to this problem was based on the concept that adequate therapy in intestinal obstruction must accomplish two things: (1) relieve the mechanical impediment; and (2) relieve the distention and remove the toxic content. In accomplishing these objectives we permit a quick return of the intestinal tract to a normal physiologic status. These principles have been applied to both the large and small bowel.

In many institutions decompressive relief of small bowel obstruction through surgical intervention has been handled well for quite some time, the criterion being that no abdominal wound shall be closed over unruly distended small bowel. The ease with which the wound can be closed serves as an excellent indicator for the need of decompressing procedures.

Moynihan[3] and Holden[4] over thirty years ago indicated that enterotomy with decompression was the procedure of choice in the therapy of small bowel obstruction. In all too many instances the problem of large bowel obstruction is still handled by multiple operative procedures.

More recently Poth[5] demonstrated that no viable bacteria could be isolated from feces following its contact for 15 minutes with Neomycin in concentrations readily maintained in the gastrointestinal tract.

The bactericidal capabilities of Neomycin have allowed us to safely extend decompressing procedures and one-stage definitive surgery to include the obstructive problems of the large bowel. Cohn,[6] in an excellent review of strangulation obstruction, clearly indicates the toxic and sometimes lethal effect of strangulated intestinal content. He has also demonstrated the effectiveness of antibiotics in combating this toxicity and prolonging the viability of the bowel proper.

We believe that the mortality rate in intestinal obstruction can be reduced and that it should approach that of elective surgery rather than the 15 to 30 per cent rate that is repeatedly reported in our surgical literature of today.

We have operated upon 45 cases of intestinal obstruction with the method to be described. At the same time we have accomplished curative resections for malignant lesions. The locations of the lesions, diagnosis and the number of each is shown in tables 1 and 2.

Technic of Operation

In cases of small bowel obstruction that present a minimal amount of distention and are of short duration, correction of the mechanical impediment may at times suffice. In other words, the abdominal wound can

TABLE 1

DIAGNOSES OF LESIONS OF SMALL BOWEL

Diagnosis	*Number of Cases*
Adhesions	11
Carcinoid	1
Endometrioma	1
Gangrene	1
Hernia internal	1
Intussusception	1
Meckel's diverticulitis metastatic carcinoma	1
Volvulus	2
Total	19

*Read before the D. C. Day Program, Fiftieth Annual Meeting of the Southern Medical Association, Washington, D. C., November 12-15, 1956.

†Courtesy of Medical Annals of the District of Columbia 26:61, 1957.

‡From Surgical Service, Garfield Memorial Hospital, Washington, D. C.

TABLE 2

DIAGNOSES OF LESIONS OF VARIOUS PORTIONS OF COLON

	Diagnosis	Number of Cases
Right	Carcinoma	5
	Carcinoma recurrent	1
	Diverticulitis	1
	Diverticulitis perforated	2
Transverse	Carcinoma	3
Left	Carcinoma	12
	Endometrioma	3
	Volvulus	1
	Total	26

be closed easily following the necessary operative procedure. These cases do not need intestinal decompression. For those remaining cases that present a sea of unruly distended intestine the problem is approached in the following manner.

Through a large right paramedian incision the distended bowel is gently delivered to the anterior abdominal wall. The decompression is initiated by dividing the distended bowel close to the collapsed segment between straight Kocher clamps. If the distention is too great for this, needle aspiration of the gaseous content will permit a safe application of the dividing clamps.

FIG. 1

Emptying of small bowel by stripping toward open end.

FIG. 2

Injection of Neomycin solution through distal bowel wall into proximal bowel.

After the bowel is divided, several centimeters of the mesentery is divided at the margin of the bowel. This will permit a tube-like portion of the obstructed segment of the bowel to be held in a sterile basin at the side of the patient. With the opened end of the bowel held firmly in place its content can be emptied from the ligament of Treitz down by gentle stripping motions as indicated in figure 1.

After the bowel is emptied, that portion of the small bowel that has been used as a tube to deliver the content into the basin is transected at the edge of the abdominal wound and dropped into the collecting basin. The assistant now removes this basin and replaces his gown and gloves prior to returning to the operating team. At no time have we noted any evidence of pulse, blood pressure or respiratory distress from this gentle stripping action on the small bowel. Extreme gentleness is exercised at all times during this procedure. Gauze sponges saturated in a 3 per cent Neomycin solution in saline are used to police the transected ends of the small bowel (1 Gm. 30 to 40 cc. saline).

This procedure provides an empty small bowel capable of early physiologic function. The distended segment recovers its intestinal tone and turgor very quickly following the decompression. One often observes motility returning to the upper jejunum while still decompressing the lower ileum. Following the decompression the continuity of the bowel can be established by an end-to-end open anastomosis. This technic will be discussed later in the paper.

When the anastomosis is completed, the entire intra-abdominal area can be sprayed with a 3 per cent Neomycin solution by using

a small gauge needle and a Luer-Lok syringe. We also place 20 cc. of the 3 per cent Neomycin in the lumen of the proximal bowel by inserting a needle through the distal bowel wall as it is held against the anastomotic stoma thereby assuring the accurate placement of the solution as demonstrated in figure 2. The total intraperitoneal dosage of Neomycin in these cases has been 1 Gm. or less and at no time have we experienced any complications from its use, including that of respiratory arrest.

The gloves of the operating team are changed prior to closing the abdominal wall over the collapsed small bowel.

Right Colon

The abdomen is entered through a right paramedian incision. If the ileocecal valve is competent and the small bowel is not distended, the specimen to be removed may serve as a container for the obstructed bowel content as demonstrated in figure 3.

In many instances with early diagnosis and operation, the obstructed bowel is only moderately distended and the entire small bowel can be emptied into the right colon by stripping maneuvers as previously described under the small bowel procedure. This can be done prior to the division of the terminal ileum and here again the specimen and its content can be removed as one procedure.

FIG. 3

Use of section of colon to be removed as reservoir for obstructed small bowel content.

In obstructing lesions of the cecum with incompetent ileocecal valve, the terminal ileum is transected at its elective anastomotic site between clamps and the proximal distention is handled as described under small bowel procedures. If there is present such a marked distention of the right colon as to interfere with its mobilization, needle aspiration or the induction of a rectal tube through the transected terminal ileum into the cecum will permit sufficient decompression for a safe mobilization procedure.

When the mobilization has been completed, the transverse colon is emptied by a reverse stripping of the bowel toward the obstructing lesion. The colon is divided at the site of election and removed. The bowel ends are cleansed with gauze sponges moistened in 3 per cent Neomycin solution. Here again, 3 per cent Neomycin is placed in the proximal bowel lumen through the completed anastomosis by a needle inserted through the distal bowel wall. Neomycin is sprayed over the abdominal cavity and the drapes and the gloves are changed prior to the abdominal closure.

Left Colon

The abdomen is entered through a left paramedian incision. On rare occasions obstructions of the left colon may present only a moderate amount of distention, permitting sufficient mobilization to use the specimen as a container. In these instances, gentle stripping of the proximal and distal bowel content into the segment to be removed will accomplish simultaneous decompression and resection. Most often this procedure is not possible due to the marked distention associated with lesions obstructing the left colon and rectosigmoid. When confronted with this problem, needle or trocar aspiration proximal to the obstructing lesion will reduce the distention to a point where mobilization of the colon may be safely accomplished.

Following the mobilization of the left colon and ligation of the inferior mesenteric vessels, a reverse stripping of the rectosigmoid area is done emptying the bowel toward the obstructing lesion. A crushing clamp is placed

FIG. 4

Emptying of bowel after ligation of inferior mesenteric vessels at point of origin.

across the bowel just proximal to the site of transection and the bowel is divided, leaving an open distal lumen which is cleansed and temporarily packed with gauze sponges moistened in 3 per cent Neomycin solution to await the anastomosis.

Ligation of the inferior mesenteric vessels at their point of origin permits the carrying of a long segment of the obstructed bowel laterally away from the operative field. A large opening is made in the distended bowel, as it is held in a sterile basin by an assistant (Fig. 4). With patience and gentleness, the intestinal tract from the jejunum down may be completely emptied. With a mobilized and decompressed left colon and sigmoid either a palliative or a curative type of resection may be done as the situation and diagnosis demand.

An open end-to-end one layer anastomosis has been accomplished in all cases. Neomycin is placed in the proximal bowel, gloves and drapes are changed, and Neomycin is sprayed over the peritoneal cavity prior to the peritonealization and closure.

Anastomosis

Since the submucosal layer of the intestine is the layer of strength and the serosal is the layer of agglutination, we must approximate these respective layers in such a way as to permit early sealing of the suture line and firm functional healing.

In multiple layer anastomosis the last layer that is so placed as to include the submucosa and approximate the serosa is responsible for the security of the anastomosis. Additional layers tend to narrow down the lumen of the bowel, or at times form an internal cuff of tissue that I am sure is responsible for many situations commonly referred to as stomal edema.

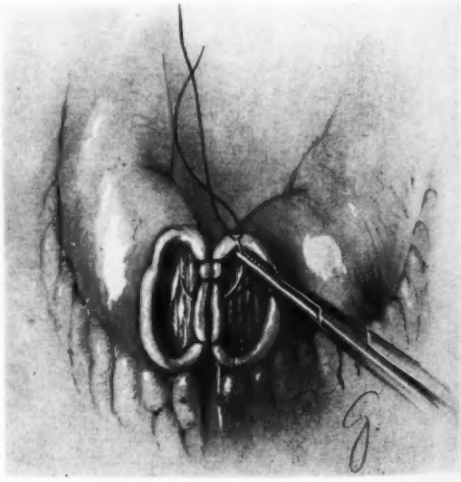
We feel that a one layer through-and-through interrupted cotton suture gives us the anastomosis that is most secure and quite capable of early function. This applies to both large and small bowel.

In the small bowel we rotate the mesenteric borders slightly so that they do not fit directly opposite each other. In the large bowel the ends are fitted comfortably and without tension.

The through-and-through stitch, forming the posterior part of the anastomosis and demonstrated in figure 5, presents no problem of placement or understanding. The same stitch can be used for almost the entire circumference of the anastomosis.

By moderate rotation the lateral angles of the anastomosis are sutured. The anterior por-

FIG. 5



Use of through-and-through stitch.

tion of the anastomosis can be sutured from the inside with the through-and-through stitch by using two spaced sutures for traction and everting this portion through the opening that remains to be closed (Fig. 6). This everting procedure cannot completely close the anastomosis, and as a usual rule one to three interrupted Connell sutures will be necessary to finish the anastomosis. In our hands this technic has been fast and secure.

Aids to Management and Care

1. Attention to fluids and electrolyte needs at all times.

2. Preoperative sigmoidoscopic and x-ray studies to include barium enema should be available at all times.

3. No barium by mouth if obstruction is suspected.

4. To surgery with gastric tube in place and suction.

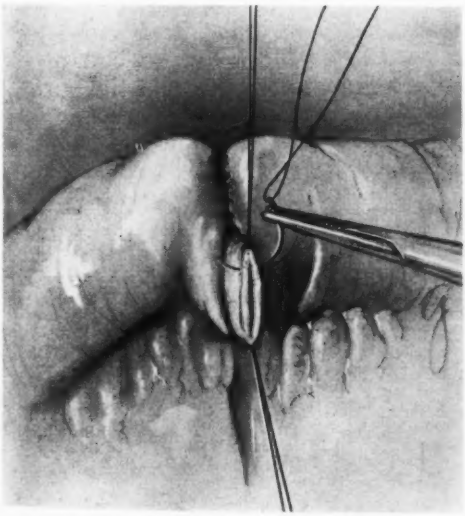
5. Endotracheal anesthesia is to be desired.

6. Contaminated tissue and instruments are maneuvered away from the operative field at all times.

7. There should be no intestinal spillage in the peritoneal cavity.

8. Gloves and drapes are changed as the anastomosis is completed.

FIG. 6



Suture of anterior portion of anastomosis from inside.

9. Neomycin is placed in the lumen and the peritoneal cavity.

10. If in doubt about the wound use through-and-through wire sutures for closure.

11. Dilate anal sphincters in all cases following surgery.

12. Neomycin is administered through a gastric tube the next day.

13. Supportive antibiotics.

14. When gas is passed per rectum the patient is started on a regular diet.

15. Patients without means of proper mastication may have a soft diet.

Causes of Death

There have been 6 deaths in this series with a mortality rate of 13.3 per cent. Briefly these deaths are as follow:

1. An obstructing carcinoma of the right colon in a patient aged 83, who died on the fourteenth postoperative day from aspiration pneumonitis. An autopsy was done, demonstrating a functional anastomosis and no evidence of peritonitis.

2. An obstructing Meckel's diverticulitis and associated metastatic lesions in the small bowel from a prior carcinoma of the colon in a patient aged 70, who died on the thirteenth postoperative day from a cardiovascular accident. The autopsy demonstrated a functional anastomosis and no evidence of peritonitis.

3. An obstructing carcinoma of the left colon in a patient aged 55, who eviscerated on the eighth postoperative day, following a left colectomy and a resection of the left lobe of the liver and spleen for metastasis. This patient underwent a secondary closure with through-and-through wire sutures to expire on the fourth postoperative day from a pulmonary infarct. The autopsy demonstrated a functional anastomosis and peritonitis with a small 3 cm. abscess in the splenic area.

4. An obstructing carcinoma of the sigmoid in a patient aged 81, that died on the twenty-third postoperative day. There was no autopsy. For religious reasons this patient refused blood transfusions and some forms of intravenous therapy. Clinically she died from anemia, hypoproteinemia and inanition. She repeatedly made the statement that she wanted to die.

5. An obstructing carcinoma of the sigmoid in a patient aged 58, who died on the first postoperative day from a myocardial infarct. (No autopsy.) This patient refused therapy and surgery for 2 days until severe abdominal distention and cramps eventually forced his consent for surgery.

6. An obstructing adhesion of the terminal ileum in a patient aged 68, who died on the eighteenth postoperative day from a pulmonary infarct. There was no autopsy.

On a close inspection of the deaths in

this series of cases, we find that five of these were directly due to associated medical complications and not as a result of the surgical procedures.

Three autopsies were done, and in two of these no evidence of peritonitis and a functional anastomosis was demonstrated. In the other case a functional anastomosis was demonstrated but there was also an associated peritonitis and an abscess in the splenic area. Technically, our surgical procedure is at fault in one case out of 45, and this was due to an evisceration of the wound on the eighth postoperative day necessitating a secondary closure, following which he expired on the fourth postoperative day from a pulmonary infarct.

We realize that this small series of cases is not conclusive but it would seem to indicate a better approach to the problem and raise the hopes for a lowered mortality rate in this particular field of surgery.

The morbidity of this series of cases may best be brought to your attention by the following facts:

1. The average hospital stay was 10 to 11 days.

2. The extremes of postoperative temperature elevations were from 98.6° to 101.8°, except for the terminal temperatures.

3. A functional bowel was present on the third postoperative day manifested by the voluntary expulsion of flatus per rectum.

4. Their ages were from 28 to 84. In addition to lowered mortality and morbidity figures, there is an economic value to be considered. Certainly, a shorter hospital stay and one trip to the operating room is far less demanding in both time and risk than multiple procedures.

Our approach to this problem of intestinal obstruction does not require elaborate or expensive equipment or special skills and is something one can readily accomplish in any hospital.

Conclusions

Morbidity and mortality rates in acute intestinal obstruction can be reduced by emergency definitive one-stage surgery.

Surgical decompression of the acutely obstructed colon as well as the small bowel is a safe and necessary procedure.

In the hands of a skilled surgeon with modern hospital facilities there should be no need for special equipment or training.

Forty-five cases of emergency definitive one-stage surgery for intestinal obstruction have been presented with one technical failure.

N. B. The illustrations for this report were made in the Department of Medical Illustration of the Georgetown University School of Medicine (B. J. Melloni, Director).

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Some Neurochemical Factors Affecting Cerebral Function and Activity*

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Physiologic activity within the central nervous system may be better understood through metabolic and enzymatic studies.

Introduction

THE CENTRAL NERVOUS SYSTEM differs from other organs of the body both in its chemical constitution and in its metabolic organization. Much of its solids consists of complex lipids and lipid-protein aggregates, a composition which, quantitatively at least, distinguishes it from the rest of the body. The blood-brain barrier mechanism imposes on the central nervous system a form of isolation or protection from the general bodily environment and stabilizes its internal milieu. The neurons have specialized in their functional activity to subserve primarily the processes of reception, conduction and transmission of impulses, which affect not only their own local scene but every aspect of bodily function. At the same time the mature neuron has departed from the general cellular pattern in its inability to reproduce itself normally or to restore function to areas pathologically deprived of neuronal perikarya. As a result of these factors and others that these imply, the central nervous system exhibits both a great dependence upon normal functioning of the body as a whole and at the same time a considerable independence of the details and variations of bodily functions. This situation is reflected in similarities or a kind of uniformity in the responses of the central nervous system to disturbances of its metabolism and function, whether these be viewed at the clinical, pathological, biochemical or cellular level.

An understanding of the factors which affect central nervous system function and activity will illuminate many problems encountered at all these levels of consideration. It is not feasible to try to cover all the factors involved. Instead it seems desirable to concentrate on the more important factors, so that the principles upon which individual situations depend can be understood and thereby provide an intelligible approach to new or different problems not considered here.

Metabolism *In Vivo*

Oxygen and Glucose. Despite the great importance of the study of cerebral metabolism *in vitro,* the results obtained must eventually be placed in perspective with metabolism of the central nervous system *in vivo,* in the intact, functioning situation. When this is done, two fundamental factors are immediately apparent: The dependence of the central nervous system on a regular, adequate supply of oxygen and on a regular, adequate supply of glucose. Under certain experimental circumstances, one or the other, or perhaps even both, of these substrates may be omitted and activity of a sort persist, but it is not normal metabolic activity nor would it support normal functional activity of the intact organism.

When the *in vivo* metabolism of the brain is compared with some other important organs of the body, data summarized in tables 1 and 2 are obtained. In considering these data, it is important to realize that there have been more studies on cerebral metabolism *in vivo* than on metabolism of other organs. Also it is difficult to make absolute comparisons, since experimental conditions vary from one study to another. Despite these qualifications, it is apparent that for its small mass (about 2 per cent of the total) the brain commands a substantial portion of the total blood flow and oxygen consumption and most of the total glucose consumption under "resting" conditions (Table 2). During muscular work,

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TABLE 1

METABOLISM IN VIVO OF VARIOUS HUMAN ORGANS

Organ and Experimental Conditions	Wt. (Kg.)*	Blood Flow ml/100g/min	Q_{O_2} μM/100g/min	$Q_{Glucose}$ μM/100g/min	Q_{O_2}/Q_G	R.Q.
Total Body—Basal	63	60	— 16.5	— 1	16.5	0.82
Brain: Normal, Awake	1.4	54	—150	— 30	5	0.99
Asleep		65	—150			0.96
Comatose		63	— 90			0.96
Skeletal Muscle—Resting	25	3.6	— 15.5	— 0.45	33	0.75
Cardiac Muscle—Normal Work	0.3	103	—445	— 27	16.5	0.75
Liver†—Normal Metabolism	1.5	14	—180	(+ 22)		

*Calculations based upon an "ideal" man of 63 Kg. body weight, 1.73 sq. M. body surface, and 40% of mass as skeletal muscle.
†Based on measurements of splanchnic circulation.
(References: 24, 131-142)

as exemplified by values for working cardiac muscle (Table 1), a much greater proportion of total blood flow, oxygen consumption, and probably glucose utilization would be channeled to skeletal muscle than under conditions of inactivity shown in table 2. In terms of blood flow and oxygen consumption the brain is equaled or surpassed by other organs, but its utilization of glucose is quite unique.

For complete oxidation of glucose to carbon dioxide and water, 6 moles of oxygen are required per mole of glucose. By comparing molar uptakes of oxygen and glucose (ratio Q_{O_2}/Q_G), as shown in table 1, the proportion of total oxygen consumed by each organ which is utilized for glucose oxidation can be estimated. Only in the case of brain is the ratio of the order of 6, indicating essentially all oxygen consumed is concerned with glucose oxidation. Other organs clearly oxidize other fuels, notably lipids, to a greater or lesser degree. This conclusion is supported by the values for respiratory quotient (R.Q. = moles O_2 consumed/moles CO_2 evolved) given in table 1, of which only that for brain approaches 1.0, the theoretical value for carbohydrate (glucose) as the sole fuel or energy substrate. Where reasonably analogous *in vitro* studies have been done, comparable R.Q. values have been obtained,[1-5] including values for liver which indicate that it does not oxidize glucose. As shown in table 1, the liver *in vivo*, normally produces glucose from its glycogen stores, so that its own metabolism is somewhat obscured under these circumstances.

TABLE 2

APPROXIMATE PERCENTAGE OF TOTAL

	Brain	Muscle	Liver
Mass	2	40	3
Blood Flow	20	25	5
O_2 Uptake	20	50	25
Glucose Uptake	65	20	

The Blood-Brain Barrier and Energy Production. The apparent "preference" of the brain for glucose as its energy substrate is in a sense an artificial preference. *In vitro* cerebral tissue can utilize other substrates such as fructose, mannose, galactose, and glutamic acid, as well as intermediates of carbohydrate metabolism,[4,6] whereas *in vivo* such substrates are unable to adequately support normal cerebral metabolism.[7,8] The explanation of this apparent paradox lies in the phenomenon of the blood-brain barrier, which permits a ready, rapid penetration of glucose into the central nervous system compartment but only slow or in some cases no apparent penetration of other substrates and metabolites.[9-12] The barrier is presumed to function as an homeostatic mechanism which maintains a more constant neuronal milieu and protects the central nervous system from the daily vicissitudes of bodily life.[13] As will become apparent subsequently, this situation has conferred on the brain a large measure of independence in terms of metabolic requirements, so that much of its structure and functional equipment is synthesized *in situ* from carbohydrate sources. However, this has also resulted in an orientation of the basic metabolism of the brain to dependence almost exclusively upon glucose, and oxygen, for its energy supplies, as shown in table 3.

When glucose is oxidized completely to carbon dioxide and water, pairs of hydrogen atoms are enzymatically removed at many steps in the process and are passed through a system of enzymes (the cytochrome system)

TABLE 3

CEREBRAL ENERGY METABOLISM

$$2\ H \xrightarrow{+\frac{1}{2}O_2} H_2O \qquad (I)$$

$-\Delta F = 52$ kg. cals. $= 2$ or $3 \sim P$

Metabolic Reaction	*Net Yield*	
1 Glucose → 6 CO_2 + 6 H_2O	32 ~ P	(II)
1 Glucose → 2 Lactic Acid	2 ~ P	(III)
1 Glutamic Acid → 1 Oxaloacetate	10 ~ P	(IV)

Substrate	*Cerebral Conc. (μM./g.)*	*Condition*	*In Vivo Survival Time (min.)*
Oxygen	0.3	Anoxia	8
Glucose + Glycogen	9.0	Hypoglycemia	90
Glutamate	15.0	Aglycemia	20 (?)

(References: 14, 15, 17, 19, 143-145)

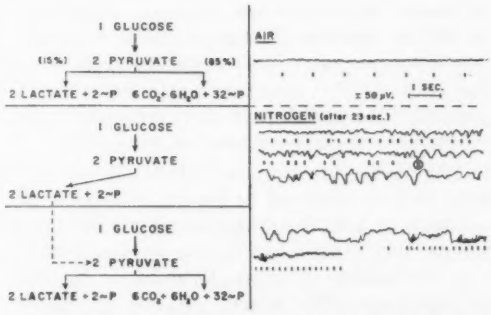
which promotes the final combination of the hydrogen pair with molecular oxygen to form water (Reaction I, Table 3). Coupled with this reaction series is the build up of cellular energy in the form of high-energy phosphate bonds (designated ~ P) in such compounds as adenosine triphosphate (ATP) and creatine phosphate. For every pair of hydrogens so treated, a free energy change (ΔF) of 52,000 calories, equivalent to formation of 2 or 3 ~ P, occurs. The high-energy phosphate bond (~ P) is, so to speak, the cell's energy currency or bank, a convenient form which it can utilize to invest in numerous cellular reactions which would not otherwise go fast enough for metabolic and functional demands.

It can be calculated and demonstrated that, for every molecule of glucose which is completely oxidized, 32 ~ P are derived for support of cellular energy requirements (Reaction II, Table 3). If no oxygen is available, glucose cannot be oxidized but undergoes only anaerobic glycolysis to lactic acid, a process which yields only 2 ~ P (Reaction III, Table 3). Similiarly if glucose is not available and some other endogenous substrate, such as glutamic acid, must be used, the ~ P yield in the presence of oxygen is much smaller (Reaction IV, Table 3). Without oxygen most alternative substrates cannot be utilized at all.

Anoxia and Hypoglycemia. When these data are applied to clinical situations, their significance is obvious, as indicated at the bottom of table 3. Anoxia from whatever cause results in rapid failure of the brain, which can no longer be revived after about 8 minutes.[14-16] This is indicative of the extreme dependence of the central nervous system upon adequate supplies of oxygen and upon the energy yield which such supplies ensure. This contrasts with other organs of the body, notably skeletal muscle, which can survive and function during much longer periods of anoxia due to the greater versatility of their metabolic organization. Similarly continuation of hypoglycemia, as induced by insulin, past the time when central nervous system stores of glucose and glycogen are exhausted also results in irreversible damage to cerebral functions. This time is approximately 90 to 105 minutes.[16,17] Other endogenously available substrates are not capable of maintaining function *intact* for any appreciable period of time.[18,19] Again this contrasts with other body tissues where utilization of lipid and protein can be resorted to with impunity for much longer periods of time. The brain calls upon these sources also, but only at the expense of its own structure.[18,19] It is poor economy to burn up the furniture to keep the house warm.

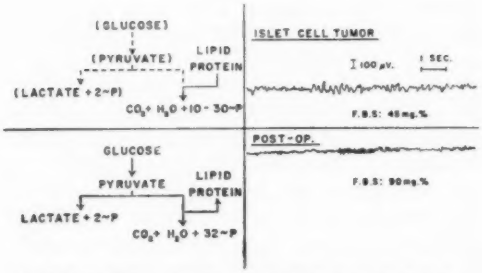
These points can be summarized by two clinical examples shown in figures 1 and 2. Under conditions of normal oxygenation, 85 per cent of the glucose utilized by the brain is oxidized completely with the concomitant production of 32 ~ P, the remaining 15 per cent undergoing aerobic glycolysis to lactic acid, as outlined in figure 1. When nitrogen is breathed instead of air, the electroencephalogram (EEG) begins to show changes within a few seconds and more or less coincident with

FIG. 1



Cerebral Anoxia. Changes in cerebral metabolism during anoxia are summarized on the left. (See text for discussion.) On the right is an EEG record (vertex to ear lead) from a human subject during air breathing and after the onset of nitrogen breathing. Interval markers below the EEG are key taps by the subject. Unconsciousness occurred at point (X), at which time air breathing was resumed. The record is continuous below the dotted line. Spikes in the recovering EEG are muscle artefacts. EEG record reproduced from Chart 5, p. 1143 of Gibbs, F. A., Davis, H., and Lennox, W. G.: *Arch. Neurol. & Psychiat.* 34:1133, 1935 (by permission of the authors and the editor).

FIG. 2



Cerebral Hypoglycemia. Changes in cerebral metabolism during hypoglycemia are summarized on the left. (See text for discussion.) On the right is an EEG record (fronto-occipital leads) of a patient with a functioning islet cell tumor before operation (above) and after removal of the tumor (below). Fasting blood sugar (FBS) values at the time of recordings are shown. (EEG record reproduced from figure 1, p. 35 of Strauss, H., and Wechsler, I. S.: *Am. J. Psychiat.* 102:34, 1945 (by permission of the authors and editor).

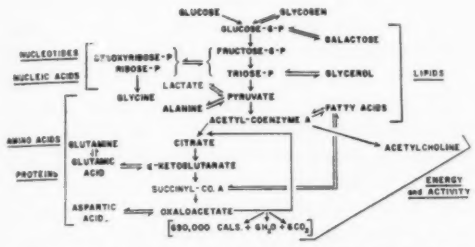
loss of consciousness the onset of high voltage slow waves. In the case illustrated, unconsciousness occurred after 35 seconds of nitrogen breathing. Deprivation of oxygen supplies results in a shift of cerebral metabolism to anaerobic glycolysis, yielding lactic acid and only a very small supply of energy. Presumably the EEG changes reflect this metabolic shift, but it is important to recognize that the cellular and metabolic basis for surface-recorded EEG's is poorly understood. When breathing of air is resumed, consciousness returns rapidly (in 11 seconds for the subject illustrated) with concomitant restoration of normal EEG patterns and a shift back to oxidative metabolism of glucose. The continuation of anoxia from whatever cause beyond the period indicated in figure 1 quickly results in irreversible changes, which are an all too familiar clinical problem. This subject has been extensively reviewed both from the clinical[15,20,21] and neuropathologic standpoints[14-16,20,22] and probably represents the oldest neurologic syndrome on record.[20]

The analogous situation, when glucose supplies fail, is outlined in figure 2. This is an example of a functioning pancreatic islet cell tumor, but similar results are obtained after experimentally- or clinically-induced insulin hypoglycemia.[23-27] When glucose is insufficiently available or completely lacking, the usual metabolic sources of cerebral energy fail. In an effort to maintain a production of energy, cerebral tissues call upon lipid and protein components to serve as substrates. Experimental verification of tissue breakdown and use of these other substrates has been obtained from the work of Geiger and associates.[18,19,28,29] A reduction in nucleic acids, phospholipids and phosphoprotein fractions exceeding 50 per cent in 60 minutes of aglycemia has been observed with a concomitant decrease in R.Q. from 1.0 to as low as 0.5, indicating consumption of lipid rather than carbohydrate fuels.[18,19] Clinically there are characteristic changes in the EEG during hypoglycemic depression or coma in the form of high voltage slow waves, as illustrated in figure 2. If glucose supplies are restored in time, the EEG reverts to normal and cerebral metabolism is able to resume its usual pattern of glucose oxidation and build up of tissue structural elements. However, if hypoglycemia persists irreversible changes occur, which again are familiar to the clinician and neuropathologist. These have been reviewed by a number of investigators.[16,30]

While the foregoing discussion is sufficiently emphatic, it may be reinforced further by a brief reference to general bodily reactions to anoxia and hypoglycemia. These have been reviewed in detail elsewhere.[31-33] Initially glycogen stores are mobilized both directly and by adrenalin secretion from the adrenal medulla to provide extra glucose. As this source fails, the pituitary-adrenal cortex system comes into action to produce adrenal cortical hormones which promote gluconeogenesis (glucose from protein) by the liver. Since it has been already indicated that the rest of the body can survive much longer without oxygen or glucose, it is reasonable to infer that these defense mechanisms are activated principally in support of cerebral metabolism and its energy production.

To paraphrase Haldane[34] anoxia and hypoglycemia not only stop production but also wreck the machinery. In the case of anoxia the failure is much swifter, since no adequate anaerobic alternatives are available. With hypoglycemia, but adequate oxygen, metabolic substitutes can be and are used, but at high cost to the structure and economy of the cell. The examples cited emphasize how dependent the central nervous system is upon adequate supplies of oxygen and glucose. They also imply that any factor which interferes at an important stage or sequence in the metabolic utilization of substrates could have equally serious consequences.

FIG. 3



Summary of Important Steps in Glucose Utilization by Cerebral Tissues. The glycolytic stage includes steps from glucose through pyruvate; the Krebs cycle includes steps from citrate through oxaloacetate. Interchanges of carbohydrate metabolites at various stages are given to indicate where structural units for lipid, nucleic acid, and protein synthesis may be derived. Complete oxidation of glucose in the Krebs cycle yields CO_2, H_2O and energy as ~ P (see text). The abbreviation P = phosphate.

Glucose Metabolism: The Concept of a Biochemical Lesion

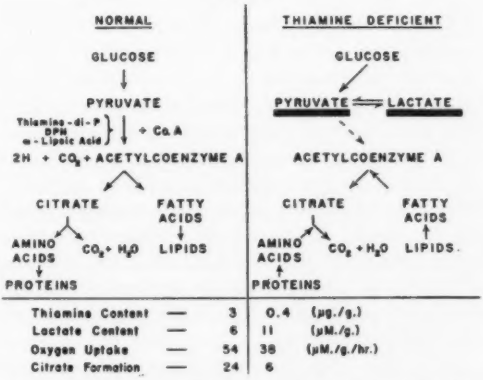
Glycolysis and the Krebs Cycle. Such situations are in fact encountered. To understand the mechanisms involved a concept of the metabolic pathways is necessary. Figure 3 represents an abbreviated version of most of the important known steps associated with the fundamental metabolism of neurons, the utilization of glucose for production of cellular energy and structural units. Glucose derived from the cerebral circulation is first carried through the stage of glycolysis, during which it is split into two triose (3-carbon) units, ending as pyruvate (or in the absence of oxygen as lactate). As indicated in figure 3, some glucose or metabolites thereof may be diverted to production of structural and functional units such as galactose, pentoses, glycerol and amino acids (glycine and alanine) for incorporation into lipid, nucleic acid and protein molecules.

In the presence of oxygen, the bulk of the glucose, as pyruvate, is further metabolized by oxidation in the Krebs citric or tricarboxylic acid cycle. Here the acetyl (or 2-carbon) unit derived from pyruvate is condensed by means of a condensing enzyme and coenzyme A with oxaloacetate of the cycle to form citrate. The Krebs cycle regenerates oxaloacetate for reception of the next acetyl unit by a series of steps which dispose of the previous two carbons as carbon dioxide and the hydrogen pairs via the cytochrome system to form water. As shown previously (Table 3), this latter process requires oxygen and is coupled with the generation of high-energy phosphate bonds (~P) as ATP or creatine phosphate. It represents the principal metabolic area where such energy production is accomplished. The necessity of oxygen for completion of this metabolic sequence explains its importance in the energy economy of the neuron. At the Krebs cycle stage also, diversion of metabolites occurs for production of structural and functional units such as fatty acids, amino acids, and acetylcholine. Other enzyme systems meshed with this basic sequence handle other amino acids, lipid and nucleotide units and integrate them into the over-all metabolic and structural demands of the cell.

With this scheme in mind it is apparent how noncarbohydrate substrates can be brought into the energy-yielding Krebs cycle during hypoglycemia. It is also apparent that interference with a number of the steps illustrated could derange the normal sequence and the production of energy or necessary structural and functional units.

The Biochemical Lesion of Thiamine Deficiency. This latter suggestion introduces the concept of a biochemical lesion, i.e., the impairment of function as a result of interruption or diversion of one or more of these metabolic steps. This concept is applicable to all tissues, but it is of interest that it grew out of studies of brain metabolism where the first such lesion was demonstrated by Peters and co-workers some 25 years ago.[35] Their work serves as an excellent illustration of the

FIG. 4



Thiamine Deficiency. The normal course of pyruvate oxidation to acetylcoenzyme A is shown on the left. The block imposed by thiamine deficiency is given on the right. (See text for discussion.) Pertinent values for normal and deficient pigeon brain are given at the bottom in micrograms (μg.) or micromoles (μM.) per gram (g.) of tissue. (References: 36-40)

characteristics of biochemical lesions, as summarized in figure 4.

Normally pyruvate, derived from glucose by glycolysis, undergoes an oxidative decarboxylation in the presence of coenzyme A to acetylcoenzyme A plus carbon dioxide and a pair of hydrogens (which are removed to the cytochrome system to form water). With production of acetylcoenzyme A, the acetyl unit can then enter the Krebs cycle, as discussed above, or be used for fatty acid and lipid syntheses. The step between pyruvate and acetylcoenzyme A is catalyzed, or facilitated, by three coenzymes, diphosphopyridine nucleotide (DPN) which accepts the hydrogen pair, thiamine-diphosphate (or co-carboxylase) which facilitates the removal of carbon dioxide from the pyruvate molecule, and α-lipoic acid which assists in the formation of acetylcoenzyme A from the remaining acetyl unit. This reaction step is a very crucial one because it represents the means by which the cell is able to go from a 3- to a 2-carbon unit, a process which is apparently rather complex metabolically for the cell.

In the presence of thiamine deficiency, this step fails because of insufficiency or absence of one of the essential coenzymes, thiamine-diphosphate, which is required for the conversion of the 3-carbon pyruvate into the 2-carbon acetyl unit. As a result, pyruvate oxidation cannot proceed, and it accumulates as such and as lactic acid. From previous discussion, it is obvious that a major consequence is failure of most of the energy yielding steps in glucose utilization, which reside in the Krebs cycle beyond the pyruvate stage (Table 3 and Figure 2). The result resembles anoxia in terms of failure of glucose oxidation and hypoglycemia in terms of failure of energy supplies from carbohydrate sources, necessitating calling in of noncarbohydrates substrates from lipids and proteins to support the Krebs cycle and energy production. These facts are numerically illustrated at the bottom of figure 4. It should be noted that thiamine in its coenzyme form is also required at the α-ketoglutarate to succinyl-coenzyme A step of the Krebs cycle (Figure 3), so that its deficiency is doubly damaging.

Clinically thiamine deficiency is associated with both central and peripheral nervous manifestations which make up the picture of beriberi, Wernicke's encephalopathy and polyneuritis. In experimental animals such as the pigeon, these can be studied in detail as Peters and his group have done.[35-41] In the full blown deficiency state such animals exhibit marked weakness, inanition, inability to fly and to maintain equilibrium, and extreme opisthotonus accompanied by seizure-like activity. If untreated death ensues with lesions of myelinated structures evident on pathological examination. Yet on injection of 25 micrograms of thiamine hydrochloride intravenously, after 1 to 2 hours these animals are sufficiently recovered to be able to fly and to behave quite normally.[41,42]

Such a story is in general representative of biochemical lesions of the central nervous system. It illustrates again the dependence of the brain on normally functioning energy metabolism and the grave consequences of interference with critical steps in that metabolism. In addition it illustrates the ready reversibility of such consequences when appropriate corrective measures are taken, provided they are taken before irreversible damage occurs. This is also an example of the importance of vitamins of the B-complex, or water-soluble group, since they function in cellular metabolism primarily as coenzymes for such metabolic steps. The vulnerability of the nervous system to deficencies of thiamine, riboflavin, nicotinamide, pyridoxine, vitamin B_{12} and others is familiar clinical testimony for this fact.

It is pertinent to note here that such studies of biochemical lesions have contributed much to our understanding of the details of normal metabolism. The work of Peters and his group on the role of thiamine in pyruvate metabolism by cerebral tissues formed the basis for the elucidation of this complex step in glucose utilization and its application to other tissues of the body. Numerous other examples of this valuable by-product of investigations of biochemical lesions cannot be covered here, but a few will appear in the course of the subsequent discussion.

Representative Biochemical Lesions

It is not possible to consider all the known or suspected biochemical lesions of the central nervous system in the space allotted to this paper, nor would this necessarily be profitable, since some of them are complex in nature or are only poorly understood at this

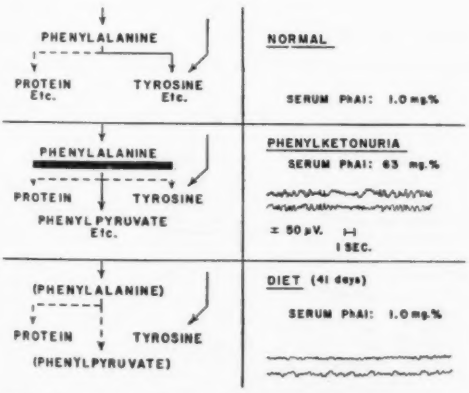
time. However, a brief discussion of several representative types of biochemical lesions may illustrate the principles involved and some of the factors which affect cerebral function and activity.

Nutritional Deficiencies. The first class of such lesions has been exemplified by thiamine deficiency. These are based upon nutritional deficiencies which deprive metabolic systems of nervous tissues of coenzymes or other similar units essential to their function and structure.

Genetic Defects. A second class of lesions arises from genetic defects. It is generally considered that individual enzymes or enzymatic steps are carried by single genes, a concept originally proposed by Garrod[43,44] and supported by work on microorganisms[45] and genetic studies of a number of clinical syndromes.[46-48] Phenylketonuria is an example of the result of such a genic and its consequent enzymic defect. This condition was first described by Fölling[49] in 1934 and has been extensively studied in subsequent years, particularly by Jervis and co-workers.[50-58] Clinically such patients exhibit mental retardation, hyperactivity, seizures and dermatitis, elevated levels of serum phenylalanine and abnormal excretion of phenylpyruvic acid and related compounds. Genetically it has been determined that the condition is due to a single autosomal recessive gene.[51,52] Biochemically this is reflected in the inability of the liver of such patients to carry out the normal conversion of ingested phenylalanine to tyrosine, a single enzymatic step involving hydroxylation of phenylalanine in the *para*-position of its phenyl moiety,[53,56,59,60] as diagrammed in figure 5. Under the circumstances, ingested phenylalanine, which is common to many foods, accumulates in blood, cerebrospinal fluid, and tissues. Disposition of the excess is accomplished mainly by the kidney, a major portion being deaminated to phenylpyruvic acid, which is excreted as such or as closely related compounds (Fig. 7). No tyrosine deficiency develops since it is also consumed in the diet, and other routes for phenylalanine utilization such as its incorporation into proteins or its conversion to norepinephrine and epinephrine are apparently unaffected.

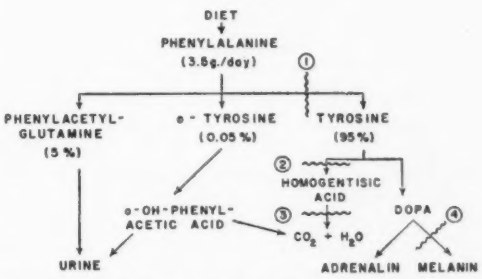
The cause of the toxicity consequent to this genetic defect in metabolism is not yet fully understood, but it is closely related to the inability of such patients to dispose of the excess phenylalanine. The recent introduction of diets with minimal amounts of phenylalanine has been attended by disappearance of all biochemical abnormalities, of the dermatitis, and of the seizures and EEG abnormalities, as well as apparent resumption of mental development.[54,58,61-65] One of the metabolites, phenylacetic acid (Figs. 6 and 7) is known to cause drowsiness, coma, convulsions and death after large doses given ex-

FIG. 5



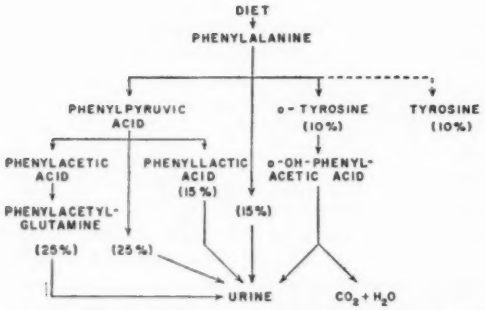
Phenylketonuria. The metabolism of phenylalanine by normal subjects (top, left), by phenylketonuric patients (middle, left), and by the latter on a phenylalanine-poor diet (bottom, left) is summarized. (See text and figures 6 and 7 for details.) On the right EEG records from a phenylketonuric patient on a normal diet and 41 days after institution of a phenylalanine-poor diet are shown. Note the prominent spikes and sharp wave activity in the former period. Serum phenylalanine (PhAl) levels are given for each period. (EEG record reproduced by permission of Dr. M. D. Armstrong of the University of Utah College of Medicine from unpublished data.)

FIG. 6



Normal Metabolic Pathways for Phenylalanine in Man. The estimated average daily intake of 3.5 grams is metabolized, in the percentages indicated, to tyrosine, *ortho*-tyrosine and phenylacetylglutamine. Further disposition of these primary products is as shown. Genetic blocks in metabolism occur at the numbered position: (1)—phenylketonuria; (2)—tyrosinosis; (3)—alkaptonuria; and (4)—albinism. Abbreviations are: o = *ortho;* OH = hydroxy; DOPA = dihydroxy-phenylalanine. (References: 43, 44, 48, 55, 56, 58-60, 66, 69, 70, 146)

FIG. 7



Metabolism of Phenylalanine by the Phenylketonuric Patient. The approximate percentages of metabolites are indicated. (References: 50, 54, 59, 67, 70, 146)

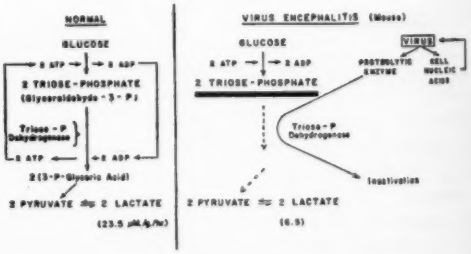
perimentally to dogs and man,[66] but the applicability of these observations to phenylketonuria is uncertain. Phenylalanine itself is not considered to be toxic[55] and experimental administration of phenylpyruvic acid has not produced toxic manifestations in kittens or aggravated symptoms of phenylketonuric patients.[51] However, these observations do not necessarily constitute proof of lack of toxicity, since the factors of duration of central nervous system exposure and age of the subject may prove to be critical.[67] It is theoretically possible that phenylpyruvic acid or one of its derivatives may interfere with pyruvate or acetate utilization by the brain or affect related metabolic steps at some stage in postnatal cerebral development. The finding that myelination is retarded in younger patients but is essentially normal in older patients[68] is pertinent to such a possibility.

Investigations of metabolic abnormalities in phenylketonuria have also provided fuller understanding of the details of phenylalanine metabolism. These are summarized in figures 6 and 7. It is interesting that there are at least four types of biochemical lesions associated with genetic defects in phenylalanine and tyrosine metabolism: phenylketonuria, tyrosinosis,[69] alkaptonuria[43,44] and albinism.[44] Locations of these enzymic blocks are shown in figure 6. The approximate disposition of phenylalanine by the phenylketonuric patient is given in figure 7. It is probable that smaller amounts of other metabolites may be excreted also.[70] No correlation between serum levels or amounts excreted and the degree of central nervous system involvement has been demonstrated.[50,70] Cerebral tissue concentrations and duration of their exposure might provide a better basis for correlation, since interposition of the blood-brain barrier makes interpretations based upon blood or urine levels difficult at best.

Phenylketonuria focuses attention on the importance of interrelationships between hepatic and cerebral metabolism, since the biochemical defect is situated in the liver but the consequences are expressed primarily in the central nervous system. Other familiar examples, such as Wilson's disease (hepatolenticular degeneration), hepatic coma and galactosemia reinforce the importance of this close association.

Neurotropic Viruses. Another type of biochemical lesion is associated with certain neurotropic viruses. The essential characteristics of this lesion are shown in figure 8. When mice are infected with Lansing strain poliomyelitis virus or Theilers FA mouse encephalitis virus, glycolysis of the infected brain tissue is markedly impaired,[71-73] as indicated in figure 8. Investigation of this finding has demonstrated that the virus is responsible for interference with a specific step in glycolysis, involving conversion of glyceraldehyde-3-phosphate to 3-phosphopyruvic acid. This is a two-stage reaction in which oxidative phosphorylation of the triose phosphate occurs followed by transfer of the high-energy phosphate bond so formed to adenosine diphosphate (ADP) to generate ATP. The enzyme catalyzing this reaction is triose phosphate dehydrogenase. In infected cerebral tissue, the

FIG. 8



Virus Encephalitis (Mouse). The effects of infection of mouse brain with Lansing strain poliomyelitis or Theilers FA mouse encephalitis virus on glycolysis and nucleic acids are summarized. Normal metabolism of glucose through the triose phosphate stage to pyruvate with its coupled phosphorylations is given on the left. The viral block due to inactivation of triose phosphate dehydrogenase is shown on the right. Respective levels of lactic acid produced during anaerobic glycolysis are given in micromoles (μM.) at the bottom. Abbreviations are: P = phosphate; ATP = adenosine triphosphate; ADP = adenosine diphosphate. References: 71-74)

neurotropic virus promotes the release from the tissue of a proteolytic (protein-splitting) enzyme which inactivates triose phosphate dehydrogenase.

Not only does this impair the further metabolism of triose phosphate and hence reduce the amount of lactic acid formed during glycolysis, but more important it disrupts the initial stages of glucose utilization. As shown in figure 8, two molecules of ATP are normally required to support metabolism of one molecule of glucose to the triose phosphate stage. These two molecules of ATP are regenerated during the oxidative phosphorylation of the two glyceraldehyde-3-phosphate molecules derived from one glucose, so that the next glucose molecule can enter the glycolytic cycle. When the enzyme responsible for this step is inactivated, the supply of ATP fails and glucose utilization is seriously impaired. Addition of crystalline triose phosphate dehydrogenase enzyme to such tissue preparations overcomes the defective metabolism. Similarly provision of creatine phosphate, as a source of ~P, also overcomes the defect.[73] Attacking the problem at a different point, the use of certain polypeptide compounds protects the enzyme from inactivation by competing with it as substrate for the virus-activated proteolysis.[71]

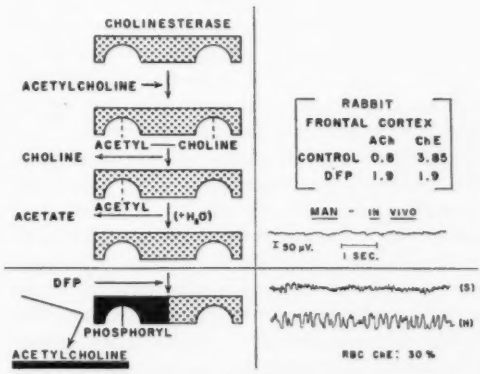
It should be emphasized that the foregoing applies to two specific viruses and their action on mouse brain. Whether this situation obtains in human cerebral tissues infected with neurotropic viruses is not known. Other actions of viruses, such as their utilization of host cell nucleic acids for their growth and multiplication must be taken into account in assessing mechanisms of virus action on the brain. However, the example given in figure 8 represents one established way in which neurotropic viruses could impair neuronal metabolism to a lethal degree.

More important this investigation has resulted in fuller understanding of the regulation of glycolysis in brain by ATP availability and the importance of the metabolic step discussed above as the rate-limiting reaction in the glycolytic cycle.[74]

Anticholinesterases. So far this discussion has dealt with biochemical lesions which affect directly or indirectly the basic energy metabolism of the central nervous system. The activity of neurons in impulse conduction and transmission is equally important to their functional effectiveness. Despite controversies and uncertainties over the role of acetylcholine as a mediator of neuronal transmission, it clearly performs this function at a majority of peripheral synapses and at a number of central synapses as well. The impairment of neuronal function by anticholinesterases such as di-isopropylfluorophosphate (DFP) supports this conclusion and provides an excellent example of a biochemical lesion in this area of neuronal activity. The situation here is summarized in figure 9.

Normally acetylcholine, released by appropriate stimulation of the neuron, is rapidly inactivated by a specific enzyme, acetylcholinesterase. As a result of the studies of Wilson and co-workers, our understanding of this enzymatic process is quite detailed.[75-80] The acetylcholine molecule is held on receptive sites of the enzyme surface as a complex, one site complexing with the choline part of the molecule and the other with the acetyl portion, as shown in figure 9. This combination permits the enzyme to split the ester linkage, releasing choline, with an acetylated enzyme

FIG. 9



Anticholinesterases. The normal steps in acetylcholine (ACh) hydrolysis by acetylcholinesterase (ChE) are shown diagrammatically (upper left). The enzyme is represented by the stippled structure with two receptive sites on which acetylcholine is complexed, as indicated by the dotted bonds. In the presence of di-isopropylfluorophosphate (DFP) the esterasic site of the enzyme is phosphorylated and thus rendered inactive, as indicated by the solid area (lower left). Acetylcholine accumulated under these circumstances, as demonstrated experimentally for the rabbit by the values given on the upper right. EEG activity in human subjects given DFP assumes epileptiform characteristics (spikes and sharp waves) in the spontaneous (S) record with build up of high voltage slow and sharp waves during hyperventilation (H). The red blood cell (RBC) acetylcholinesterase activity at the time of the EEG recordings was about 30 per cent of control values. (EEG records are reproduced from figures 1 and 2, pp. 258 and 259 of Grob, D., Harvey, A. M., Langworthy, O. R., and Lilienthal, J. L., Jr.: *Bull. Johns Hopkins Hosp.* 81:257, 1947 (by permission of the authors and editor). Other references: 75-80, 147)

remaining. The acetyl group is then easily removed as acetate by addition of water to reconstitute the enzyme for the next acetylcholine molecule.[79]

When an anticholinesterase such as DFP is present, this sequence of events is prevented. The phosphate moiety of DFP complexes with the esterasic site on the enzyme to form a phosphorylated enzyme. The phosphoryl group is so slowly removed by water, or other mechanisms at the cell's disposal, that the cholinesterase is in effect irreversibly inactivated.[75,76,78] Consequently, acetylcholine, released in the normal course of neuronal activity, accumulates and symptoms of acetylcholine excess occur, such as peripheral hyperactivity of cholinergic nerves in the form of muscle twitching, gastrointestinal and vasomotor phenomena and central hyperactivity as seizures and mental disturbances. With continuing accumulation of acetylcholine, respiratory paralysis, coma and death ensue.[81-85] The effectiveness of the so-called nerve gases and the toxicity to animals and man of numerous organo-phosphorus insecticides are practical examples of this biochemical lesion. Some representative data for DFP toxicity are included in figure 9.

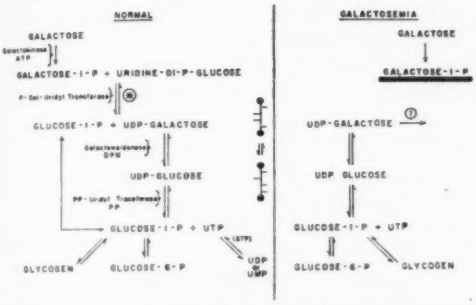
Without pharmacologic assistance, the intoxicated organism has no swift way of coping with the situation. Atropine and anticonvulsant drugs will, if used promptly, minimize the acute symptoms. Synthesis of new cholinesterase molecules to replace those inactivated by the toxic agent is, however, a slow process. In the rat regeneration in brain is at the rate of 4 per cent per day for the first two weeks and 0.4 per cent per day thereafter with some 140 days required for return to control values.[86] From a study of the characteristics of the cholinesterase mechanism, Wilson[77,80] has developed antidotes, in the form of certain hydroxyl amine derivatives, which facilitate removal of the phosphate group from the inactivated enzyme and permit its reactivation. Experimentally, at least, such compounds have proved effective in combatting the toxicity of DFP and related compounds.[80] Their clinical value is not yet known.

Nucleotides. Recently another factor in cerebral metabolism has come into prominence, one which involves the functions of nucleotides. The nucleotides are molecules made up from certain vitamins such as nicotinamide and riboflavin, from purines such as adenine and guanine, and from pyrimidines such as uracil, cytosine and thymine by the addition of a 5-carbon sugar or pentose side chain and one or more phosphates to the pentose. Adenosine triphosphate (ATP) and diphosphopyridine nucleotide (DPN) are familiar examples. The nucleotides subserve two principal functions: on the one hand they are aggregated into nucleotide polymers or nucleic acids, which are important in the protein economy of the cell, and on the other they function as such as coenzymes or facilitators of numerous enzyme reactions. While their importance to metabolism in general and to cerebral metabolism in particular has been recognized for some time, specific biochemical lesions (other than vitamin deficiencies) attributable to impairment of their function are recent developments. Two examples are given below which illustrate this point.

Galactosemia is a relatively rare syndrome, characterized by inability of the patient to metabolize ingested lactose or galactose. The condition was first described by Von Reuss[87] and by Göppert[88] and has been reviewed by a number of investigators.[89-92] Clinically severe mental retardation, high serum galactose levels, galactosuria, and usually hepatic cirrhosis and cataracts are typically found.[92] Genetic studies indicate that it results from a homozygous recessive gene.[93] Although it was recognized early that omission of galactose from the diet would stop progression of symptoms, the exact nature of the biochemical defect has only recently been elucidated. The problem is outlined in figure 10.

Normally, ingested galactose is converted in liver, red blood cells and possibly other organs by a series of steps to glucose. The conversion requires several enzymes, as shown in figure 10, plus the nucleotide coenzyme, uridine-diphosphate-glucose, derived from the pyrimidine, uracil.[94-101] After initial phosphorylation to galactose-1-phosphate, the latter, by a transfer reaction, combines with the nucleotide as uridine-diphosphate-galactose. In this form galactose can be acted upon by galactowaldenase, an enzyme which accomplishes the shift of the hydroxyl group of carbon atom 4 from the "left" to the "right" side of the molecule in the spatial configuration shown (center, Fig. 10), thus converting it to

FIG. 10



Galactosemia. The metabolism of galactose by normal human subjects is shown on the left. See text for details. The galactowaldenase inversion reaction is schematically represented (center of the figure) by the 6-carbon chain with spatial positions of the substituent OH groups of each carbon indicated by side arms. The inversion occurs at carbon atom 4, as shown. Note that the enzyme catalyzing the second reaction (denoted by the asterisk) is apparently absent from brain, so that galactose for structural units is presumable derived from glucose-1-phosphate by the subsequent reversible reactions to UDP—galactose. The situation in galactosemia is shown on the right, where the enzyme (denoted by the asterisk) is absent from all tissues, resulting in accumulation of galactose-1-phosphate. ATP = adenosine triphosphate; Gal. = galactose; DPN = diphosphopyridine nucleotide; UDP = uridine diphosphate; PP = pyrophosphate; UTP = uridine triphosphate; UMP = uridine monophosphate. (References: 94-102, 106)

glucose. As indicated, all of these reactions, except galactokinase, are reversible, so that synthesis of galactose from glucose can be accomplished when required by certain tissues such as mammary gland and brain (for galactolipid or cerebroside formation).

The inability of the galactosemic patient to convert galactose to glucose resides in the genetic defect of the second enzyme, P-galactose-uridyl-transferase, resulting in a piling up of galactose and galactose-1-phosphate which cannot be metabolized further.[96,102] Clinically this problem can be overcome by feeding galactose-free diets to such patients.[88,91,92] The exact nature of the toxicity to nervous tissues and lense is not yet known. It has been shown that a high galactose diet is toxic to chickens and pigeons, resulting in convulsions and death,[103,104] with demonstrable lesions of myelinated structures,[104] and causes cataract development in the rat.[105,106] It has been suggested that the accumulation of galactose-1-phosphate may be responsible by means of an interference with glucose metabolism,[102,106] but this possibility remains to be proved.

Azauracil. The preceding example illustrated indirectly the importance of a nucleotide coenzyme in cerebral metabolism and function. Studies now in progress with azauracil may provide more direct evidence. Azauracil is an analogue of the pyrimidine, uracil, in which one carbon atom in the ring has been replaced by a nitrogen atom (Fig. 12). The compound has been synthesized and studied independently by two groups of investigators and found to have both bacteriostatic and antitumor activities.[107-112] These studies have suggested that azauracil can be synthesized by the organism into azauridine nucleotides, which may compete with or block the action of the normal uridine nucleotides at some metabolic site.[109,110,112]

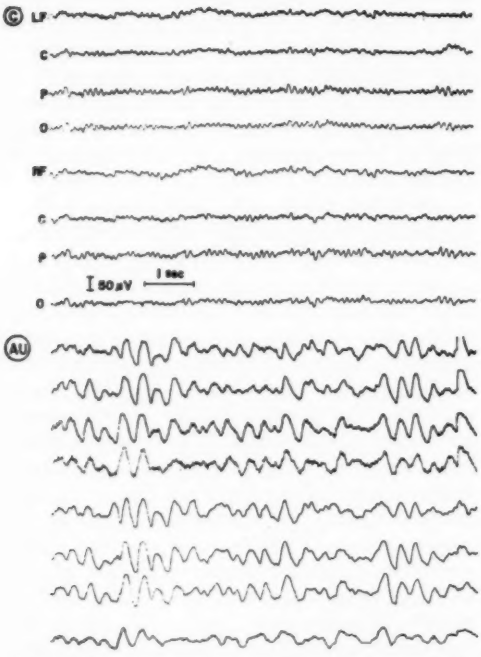
Because of its antitumor action in animals with experimentally induced neoplasms, trials have been begun in man by several groups.[111,113,114] In the course of these trials consistent side effects referable to the central nervous system have been encountered.* Clinically these consist of drowsiness and somnolence (? coma) with large doses and hallucinatory phenomena at lower chronic doses.[114] Electroencephalograms recorded from these patients show high voltage slow waves, whose appearance precedes the onset of clinical manifestations of drowsiness.[115] Such a record is illustrated in figure 11. These findings have been independently corroborated.[113] The clinical symptoms and EEG changes are readily reversible on stopping administration of the compound.

It is pertinent to note that other uracil derivatives, the antithyroid agents of the thiouracil group, have not been reported to exhibit these side effects,[116] nor have they been observed with the use of other antitumor agents, such as nitrogen mustards, mercaptopurines or folic acid antagonists,[116] although these latter agents are known to be toxic to the developing nervous system *in utero*.[117] Pyrimidines are structurally related to barbiturates and the anticonvulsant, primidone (Mysoline), is a substituted pyrimidine. However, barbituric acid and uracil themselves do not appear to exhibit any central depressant action.[116]

The biochemical basis for the cerebral toxicity of azauracil is unknown, but its effects raise several important points. The known functions of the pyrimidine nucleotides in the

*The author is greatly indebted to Dr. Charles Zubrod, Dr. Emil Frei and their associates of the National Cancer Institute, Bethesda, Md., to Dr. Arnold Welch of the Department of Pharmacology, Yale University School of Medicine, New Haven, Conn., and Dr. Cosimo Ajmone-Marsan and Dr. Charles Wells of the National Institute of Neurological Diseases and Blindness, Bethesda, Md., for their kindness in giving permission to discuss their unpublished data.

FIG. 11

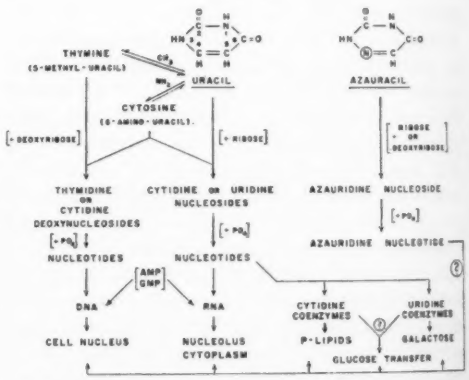


The Effect of Azauracil on the Human Electroencephalogram. The records are taken from patient J. B., girl, age 11 yrs., with myelocytic leukemia. At the top is the control record (C) with leads referred to the appropriate ear from right (R) and left (L) frontal (F), central (C), parietal (P), and occipital (O) locations. This record is considered to be within normal limits. At the bottom is a record (AU) with the same leads after 9 days on azauracil 225-450 mg. per day orally. After stopping the drug, the record reverted to the normal appearance seen in the control record above. (EEG records reproduced by permission of Dr. C. Ajmone-Marson, Dr. C. E. Wells and Dr. E. Frei, National Institutes of Health, from unpublished data.)

central nervous system are summarized in figure 12. The three principal pyrimidines are interconvertible, as indicated, and are utilized primarily as the nucleosides (formed by addition of ribose or deoxyribose to the 3-position in the ring) and as the nucleotides (formed by phosphorylation of the pentose side chain with one or more phosphate groups). Folic acid and vitamin B_{12} are concerned in a number of these reactions. As the nucleotides, they may be utilized for the formation, together with purine nucleotides, of nucleic acids and nucleoproteins. The deoxyribonucleic acids (DNA) are localized in cell nuclei, where they are concerned with nuclear chromatin and the genetic constitution of the cell. DNA and DN-proteins may also function in cellular protein synthesis. The ribonucleic acids (RNA) and their protein complexes are situated in the nucleolus and cytoplasm. Neurons are particularly rich in RNA and RN-proteins, having prominent nucleoli and Nissl bodies, the cytological representation of cytoplasmic RNA and RN-proteins. The latter are the primary sites of protein and enzyme-protein synthesis.[118-122]

In addition to these important functions, the nucleotides also serve as coenzymes. The uridine nucleotide coenzymes are necessary for galactose metabolism, as has been discussed above.[95,98] Similarly the cytidine nucleotide coenzymes are required for phospholipid metabolism.[123,124] These functions have been confirmed by Geiger and co-workers in experiments on the perfused mammalian brain *in situ*[18,19,28,29,125] In such a preparation breakdown of galactolipids (cerebrosides) and phospholipids occurs unless uridine and cytidine are added to the perfusate.[125] However, these studies suggest another role, or related function, for these nucleosides, since in their absence the permeability of the brain to glucose, or its ability to utilize glucose, is lost under these experimental conditions. Readdition of the two nucleosides to the perfusate restores normal carbohydrate utilization and metabolism. This function has been tentatively designated in figure 12 as glucose transfer.

FIG. 12



Pyrimidine Nucleotides and Azauracil. The known pathways of pyrimidine utilization by cerebral tissues are shown on the left for uracil, cytosine, and thymine. See text for discussion. (Analogous pathways are present for the purines, adenine and guanine.) The structure of azauracil is shown on the right. Note that it differs from uracil only in substitution of a nitrogen (N) atom for the usual carbon (C) at position 4 in the ring, as indicated by the encircled N. The presumed route of azauracil utilization and its possible sites of action are indicated, as discussed in the text. Abbreviations are: P = phosphate; DNA = deoxyribonucleic acids; RNA = ribonucleic acids; AMP = adenosine monophosphate; GMP = guanosine monophosphate. (References: 95, 98, 107-112, 118-125)

It is not known whether brain can synthesize the pyrimidine nucleotides from the pyrimidines themselves or whether they must be provided in the nucleoside form. Under Geiger's experimental conditions, the latter appears to be the case, but the applicability of these results to the normal *in vivo* situation cannot be assessed at present. The introduction of azauracil would appear to result in interference with one or more of the functions of the uridine and/or cytidine nucleotides, as suggested schematically in figure 12. Whatever the biochemical lesion may be, it produces striking alterations in central nervous system function. The elucidation of the nature of this lesion should add appreciably to our knowledge of the importance of nucleotides in cerebral metabolism and activity.

Seizures. Biochemical abnormalities may not necessarily be restricted to a single system or metabolic sequence. This is illustrated by the situation in cerebral seizures, where a biochemical lesion has been demonstrated to be composed of defects in or impairments of acetylcholine, glutamic acid and potassium metabolism.[42,126-130] That these may all stem from a basic or underlying lesion, perhaps in energy metabolism, has been suggested.[127,128] The various defects can be reversed *in vitro* by various metabolites, such as asparagine, and the use of asparagine clinically has been attended by an encouraging measure of success.[42,127,128] However, it would be premature to conclude that such findings and results constitute proof of the biochemical lesion responsible for seizures or of the clinical correction of this lesion. In a sense the very complexity of the lesion makes it difficult to arrive at a full understanding of the mechanisms responsible for seizures until further work can be completed.

Summary

In this somewhat selective discussion an attempt has been made to point out and illustrate some of the important neurochemical factors which affect cerebral metabolism and function. The concept of the biochemical lesion has been employed as a useful approach to the consideration of these factors. Like any concept it has its limitations and should not be used to the exclusion of others. It is too much to expect that neurochemistry will be the answer to all the problems with which the neurologist and the neuropathologist must contend. Nevertheless, the preceding discussions illuminate many of these problems and may provide a basis for understanding others which still remain to be solved. Rational correction and therapy of central nervous system dysfunctions cannot be easily achieved without such understanding. Thiamine deficiency, phenylketonuria, cholinesterase inhibition, and galactosemia illustrate this point.

Emphasis has been placed upon the importance of adequate, normally functioning energy metabolism, since this is basic to the economy of the neuron. Oxygen and glucose in continued, abundant supply and proper levels of coenzymes and the optimal vitamin and purine-pyrimidine nutrition that they imply are all essential. These factors depend upon the somewhat specialized metabolic structure and functional activity which the central nervous system has evolved behind the blood-brain barrier, and the consequences which this situation requires in normal functioning of other bodily organs such as liver and kidney.

The relative lack of versatility in metabolism renders the central nervous system peculiarly vulnerable to a variety of agents or conditions which can at one point or another upset its delicate metabolic balance. It is not surprising that both clinically and neuropathologically the responses to such a variety of conditions appear to be grossly or superficially similar, even though the individual mechanisms involved may be numerous and varied. Coma from anoxia, hypoglycemia, thiamine deficiency, virus encephalitis, diabetes and perhaps azauracil may all affect carbohydrate metabolism with similar clinical and neuropathological consequences, but the mechanisms or points of defective metabolism are individual and distinct. Seizures can be associated with anticholinesterases, pyridoxine deficiency, fluoroacetate poisoning, anoxia, phenylketonuria and numerous other causes, all of which affect different primary metabolic loci, but the resulting dysfunctions are clinically essentially the same.

The understanding of the factors which underlie such paradoxes is important, for only with a clear appreciation of these factors will it be possible to place conditions of dysfunction in their proper perspective. Much has been learned about the metabolic and func-

tional constitution of the central nervous system and the neuron through study of such conditions. The application of this knowledge to other problems with eventual elucidation of a more complete picture of factors important to cerebral metabolism and function will yield a big return in the rational prevention and treatment of many neurological problems which now confront us.

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Rectal Incontinence: Its Relation to Abscesses, Fistulas and Injuries*

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Rectal incontinence is a distressing problem for the patient and often a perplexing one to the surgeon. After giving consideration to the pathogenetic and the anatomic aspects of the situation the author outlines the management.

SATISFACTORY FUNCTION of the terminal bowel depends to a large extent upon the structural integrity of the anorectum and accessory muscles, including, of course, a normal nerve supply. It is assumed that the normal structure and function of the lower bowel and associated muscles, and pathologic influences which may be involved, are already understood because they are too complex and extensive to be described here. This discussion will be limited to some of the more frequent conditions which may lead to incontinence. Methods of prevention and some corrective procedures will also be presented.

Most cases of rectal incontinence are accounted for by one or more of the following three conditions:

1. Traumatic disruption from external or internal injury, including parturition.

2. Uncontrolled virulent anorectal infections with suppuration and necrosis of essential structures.

3. Injudicious or unskilled anorectal operations, usually for abscesses or fistulas.

The first and second of the above conditions are less frequently responsible than the third. Most of the cases are iatrogenic as unfortunate surgical results. Such failures are rare in the practice of the skilled proctologist who knows and understands the important principles of proctologic surgery.

Pathogenesis of Rectal Abscesses and Fistulas

Simple subcutaneous infections and *abscesses,* such as folliculitis, hidradenitis and infected sebaceous cysts may occur in the perianal area the same as elsewhere. Their importance is chiefly that of differential diagnosis which is not always easy. Even pilonidal cyst abscesses in some instances closely resemble infections of anorectal origin.

Proctologists generally agree that typical anorectal abscesses and fistulas are the results of the following sequence of events:

1. Initial pyogenic infection of an anal crypt (of Morgagni). Associated anal ducts and glands may also be involved.

2. Penetration of infection through the anorectal integument into adjacent structures. This forms the primary opening of the abscess and fistula which are to follow. The path of this invasion and the location of the subsequent abscess and fistula will be determined largely by local and regional factors such as extent and arrangement of associated anal ducts and glands, the disposition of muscular and fascial planes, and the blood and lymphatic supplies.

3. Suppuration and necrosis (abscess formation) in soft tissues adjacent to the anorectum.

4. Burrowing of pus along paths of least resistance. This is usually, but not always, toward the skin where, in the absence of surgical intervention, the abscess "points" and ruptures spontaneously. This forms the secondary opening and the abscess becomes a fistula.

It is obvious that for anatomic reasons these abscesses and fistulas practically always involve the sphincter muscles to some degree. This involvement in the majority of instances is not sufficient to be much of a problem to the proctologist. In some cases, however, the infection is so virulent and spreads with such destructive rapidity, that suppuration and necrosis may quickly involve and destroy extensive perirectal areas including essential muscular structures. The same extensive damage may occur more slowly in the neglected case in which the patient does not seek, or perhaps refuses proper attention.

Another reason for extensive perirectal damage is antibiotic therapy. Any attempt to abort or prevent anorectal abscess formation by the use of antibiotics is a great mistake.

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Once the "break-through" has occurred an abscess is almost inevitable. Antibiotic therapy in these cases is not only useless, but actually may be dangerous by interfering with normal processes of localization and "pointing," and by delaying essential surgical treatment. This permits slow and insiduous spread of infection and is likely to allow a relatively simple condition to become a much more serious one.

Types of Infection. Nearly all acute anorectal infections are pyogenic. The staphylococcal, streptococcal and the colon bacillary groups are among the most frequent invaders. Mixed infection is usual, but an occasional abscess may yield a pure culture of one of the above groups.

Tuberculosis inflammation is found in less than 3 per cent of all fistulas and is rarely found in acute abscesses. Its occurrence in fistulas is nearly always secondary in an original pyogenic lesion, the specific organisms usually being conveyed by swallowed sputum.

It is notable that the incidence of acute anorectal infections, including abscesses, generally parallels the incidence of acute upper respiratory infections. Acute appendicitis follows a similar pattern of relationship. When large numbers of virulent pathogens are swallowed, any vulnerable gastrointestinal structure may be attacked. Coughing, with its piston-like effect on the anorectum, may increase the hazard of infection of the terminal bowel.

Abscesses and fistulas may also be caused by traumatic perforation of sharp objects, either swallowed or from without. Direct extension of infection from nearby structures occasionally initiates perirectal suppuration which "points" and ruptures spontaneously into the lower bowel. These situations do not come within the scope of this paper.

Management of Acute Abscesses

The treatment of rectal abscesses is surgical and should be instituted as early as possible. Attempts at conservative treatment by drugs or poultices, or by the use of antibiotics are not justified because failure is inevitable, and the delay involved can be highly detrimental to the patient. It is also a mistake to wait for fluctuation to appear, or for "pointing."

Operation should be done under complete anesthesia at the earliest feasible time after anorectal cellulitis can be detected by palpation. By this time central necrosis and suppuration have already started although fluctuation may not be apparent. The primary opening should be located if possible and extirpated along with any connecting sinus tracts, anal ducts or glands. Any cavities from necrosis or suppuration should be "uncapped" and properly drained in accordance with good proctologic practice.

While the early one-stage operation, as outlined above, is the treatment of choice, it is not always possible or practicable because of unavoidable delays. In any event the abscess should be incised and drained at the earliest possible time even if this has to be done by a simple stab incision. It is highly desirable to immediately relieve the internal pressure of the abscess, even if only by partial drainage, to prevent further spread and tissue destruction. When management of this kind is necessary the patient should understand that he will have a fistula and that curative surgery under anesthesia will be required.

Management of Fistulas

An anorectal fistula is, strictly speaking, a chronic anorectal abscess which has collapsed because of drainage of its purulent content. It continues to have its initial primary opening in the bowel, usually in a crypt at the anorectal line, and one or more secondary openings usually through the external skin. The treatment of fisulas, like that of abscesses, is surgical.

The great majority of rectal fistulas can be cured by a single operation. A small proportion, however, are so complex or involve the anal control mechanism so deeply, that a multiple stage procedure (seldom more than two) may be required in order to avoid incontinence. In extremely rare instances a preliminary temporary diverting colostomy may be desirable.

In the multiple stage fistulectomy it is desired to do as much curative surgery as can safely be done during the first stage, leaving intact enough anal ring to maintain its integrity. The use of a heavy silk seton tied loosely around this remaining anal bridge is sometimes helpful in maintaining identity and simplicity of the remaining fistula for which a further operation is to be done later. Subsequent stages of the operation are delayed until

sufficient healing has occurred to give adequate peripheral support to the anal ring and to the sphincter muscles. Then the remaining anal bridge about which a seton may have been tied can be safely divided without fear of muscle separation and incontinence.

Proper postoperative care is an essential part of fistula management. Frequent inspection and minor wound revisions as indicated are necessary to obtain satisfactory results. The prevention of "bridging" is especially important so that the surgical wounds will heal firmly from the bottom.

Rectal Incontinence

The mechanism of normal rectal function should be well understood before approaching the subject of incontinence. Time does not permit detailed discussion of this important and interesting subject, but some essential points will be mentioned.

Continence of the lower bowel depends to a very large extent on the opposing actions of two separate muscular elements, each of which partly encircles the anorectum in a sling-like manner. The superficial portion of the external sphincter muscle encircles the anus anteriorly, and because of its attachment to the coccyx posteriorly, pulls the lower anus backward, and produces lateral pressure at the same time. The opposing and even more powerful sling is the puborectalis portion of the levator ani. This muscle exerts a powerful forward pull on the upper anus and also produces lateral pressure. This accounts for the almost right angle relationship of the anal canal to the lower rectum which is necessary for normal control of the lower bowel content.

It should be remembered that "rectal continence" is a relative term. The structural and functional disposition of the normal rectal outlet does not insure gas and liquid tightness. Indeed, the normal sphincter mechanism can, on occasion, be temperamental beyond comprehension, to the consternation and embarrassment of its owner! This is especially true when the rectal content is gas or a liquid such as mucus or mineral oil.

On the other hand, many individuals who have sustained rather extensive permanent damage to the sphincter mechanism by injury or disease have remarkably good control so long as their intestinal propulsive function is within normal limits and so long as they can avoid excessive gas or liquid bowel content. The patient with a properly constructed colostomy also does quite well under similar circumstances.

Interruption of essential muscle function, particularly that of the superficial external sphincter and the puborectalis, prevents normal control of the rectal content. The degree of incontinence may vary between wide limits. It may be complete, as follows the unrepaired complete rectovaginal laceration of childbirth, or very mild, such as occasional escape of gas or seepage of mucus through a small residual defect that might follow a superficial fistulectomy. Any degree of incontinence between these extremes may occur, depending upon the extent of sphincter incapacity and somewhat upon the disposition of the patient.

Deep and destructive anterior rectal abscesses, particularly in the female, are especially apt to lead to incontinence. The hazard is greater in this location because the superficial transverse perineal muscles tend to pull the structures apart in the midline so that normal apposition and healing do not occur. The same mechanism obtains in the complete perineal laceration of childbirth. Rectovaginal abscesses which progress to rectovaginal fistulas create a situation potentially as serious as the complete laceration.

Correction of Incontinence

Surgical correction of the complete perineal laceration can be done most satisfactorily by a meticulous dissection of the involved structures followed by accurate anatomic repair. Suture material should be fine chromic catgut or, even better, alloy steel wire. It is advantageous to protect the anterior anorectal portion of the repair with a sliding musculomucosal graft which has been well mobilized to avoid tension. The patient should have preoperative preparation as for colon surgery.

Rectovaginal fistulas should be cut through completely in those patients with thin rectovaginal septa and inadequate perineal structures. Then the dissection and repair can proceed as outlined above with much greater satisfaction than could be achieved by trying to repair the fistula in a thin, delicate rectovaginal septum.

In the nulliparous female, however, and in

multipara with adequate perineal and rectovaginal structures, rectovaginal fistulectomy followed by repair and overgrafting of the rectal opening with a well-mobilized musculomucosal flap is a highly satisfactory operation. This is essentially the same procedure described by Donald R. Laird in 1948. The same principle can be applied with advantage to obliterate other high fistulous openings in the bowel provided, of course, that such cases are properly selected and that related pathologic conditions can be managed satisfactorily.

Sphincter defects occurring in the lateral and posterior areas are usually in the form of cavernous scars. The most frequent cause of this type of deformity is fistula or abscess surgery followed by too much packing for too long a time. Repair of such defects can be accomplished through a curved skin incision about 5 or 6 cm. from and parallel with the anal margin. A full thickness skin flap large enough to expose the defect is turned medialward over the anal orifice and the muscle ends are identified. They must be dissected free of the scar tissue in which they are embedded and sufficiently mobilized to permit proper anatomic repair without undue tension. It is highly desirable to leave sufficient scar tissue on the muscle ends to permit accurate approximation without fear of the suture cutting through. Alloy steel wire used as a double figure-of-eight mattress suture serves well for this purpose. The skin flap is then replaced and the incision closed without drains. Healing *per primam* can be expected if proper aseptic technic has been used.

Conclusions

The surgical treatment of rectal abscesses and fistulas is especially intriguing because of the almost limitless number of variables encountered. Many of these variables offer challenges to the knowledge and skill of the surgeon and to his ability to improvise procedures to correct conditions "not found in the book."

Optimum Time for Surgery in Pelvic Inflammatory Disease*

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The time for surgical treatment and its extent has always been a debated question in pelvic surgery. The advent of the antibiotics has not resolved the question.

THE PAUCITY OF REPORTS dealing with the management of pelvic inflammatory disease during the past few years might lead to the belief that this disease no longer presents a problem. Even though many improvements have been realized through the widespread use of antibiotics, this condition continues to be the most commonly encountered problem on the charity services of most teaching hospitals.

It is not the purpose of this report to review the etiology of pelvic inflammatory disease or to discuss the well-worn subject of routes of infection and pathology, but to reflect upon our experiences as to the use of surgery in its management. It is not only important to consider if surgery is to be employed and if so, the type of operation, but equally as important is the time selected for operative intervention. Efforts to determine the ideal time for operation in the treatment of pelvic inflammatory disease are not new.

Prior to 1909, it was considered proper to operate upon these patients in the acute inflammatory stage. As a result of this practice the operative mortality was approximately 20 per cent. In 1909, Simpson[1] advocated the delay of surgical intervention until the acute phase had subsided and the patient had remained afebrile for at least three weeks in spite of repeated pelvic examinations. In his series of 456 patients managed in this manner, there was an operative mortality of less than 1 per cent. This idea of allowing a "cooling off" period completely revolutionized the surgical approach to pelvic inflammatory disease. Miller[2] in his analysis of 6,184 cases of pelvic inflammatory disease at the Charity Hospital of Louisiana reported a mortality rate of 4.2 per cent in the group of patients who had immediate surgery without a "cooling off" period, and less than 1 per cent in those who were allowed to "cool off." He advocated the approach originally set forth by Simpson, and felt that immediate operation was only justifiable in the patient who would not accept prolonged periods of bed rest.

This general conservative attitude had prevailed even to the present time, and only recently have questions arisen as to the influence of antibiotics on this dictum. As might be expected, the time-honored policies might be altered as a result of broad spectrum antibiotic therapy, improved preoperative and postoperative care, especially as regards water and electrolyte balance and whole blood transfusions. The administration of cortisone has also been advocated as a means of making earlier surgery possible.[3] These questions, in addition to an awareness of the gradual evolution to earlier, more complete surgery on our service, have stimulated the present study.

Material

The dicussion and opinions presented in this paper are derived from a review of records of 309 patients with either tubo-ovarian or pelvic abscess on the teaching service of the City of Memphis Hospitals. Ninety per cent of these patients were Negroes. This study includes only those patients with abscess formation who were managed surgically. It does not include the vast majority of patients with pelvic inflammatory disease who responded to antibiotic therapy.

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Surgical Management

The surgical management of this condition may be divided under the following headings: (1) colpotomy; (2) secondary pelvic surgery, subsequent to colpotomy; and (3) primary definitive surgery, either incomplete or total removal of uterus, tubes, and ovaries.

Theoretically, the opportune time for surgery for pelvic inflammatory disease is after the childbearing age has passed, and when the activity of the infection has abated naturally or as a result of treatment with antibiotics and other agents. The necessity for operation in younger women of childbearing age, and the resistance of abscesses to treatment often requires surgical treatment under less than opportune circumstances.

It seems to us that this has resulted in several attitudes toward surgical management of this condition. The first is incomplete operative treatment which means the removal of the most diseased tissues and leaving those that are least diseased. This may invite surgery that is otherwise avoidable.

The second is the severance of the tubes from the uterus to avoid reinfection. This has been advocated by Falk.[4,5] Though we cannot speak from extensive observation, it appears that this has not been accepted by many gynecologists. It is based on the theory that the infection in the tubes and ovaries is maintained by reinfection, and that as a result of blocking this route the disease will subside.

The third principle is an extension of the above except that the uterus is removed leaving the tubes and ovaries. This, of course, closes the pathway to reinfection and relieves the patient of the menstrual disturbances associated with inflammatory disease. We have not had the opportunity to evaluate this practice.

Fourth, and finally, the "all or none" principle, which means either using all measures short of operation or completely removing all the pelvic organs. This is based on the idea that only complete surgical removal cures the patient, and, therefore, the pelvis should be entered only when satisfied that this will be justifiable. We hasten to add that this is not done blindly, for should the diagnosis of panpelvic inflammatory disease not be confirmed at the time of surgery, exercise of judgment is paramount. This leads to many pressing questions, whether, at times, in the "teenagers" and in patients in their twenties it would not be better to leave a questionable or borderline ovary with the calculated risk of a second operation at a future date. Though this is true, the strength of this teaching is felt in the avoidance of many operations that otherwise would have been done.

Analyses of these four schools of thought reveal that when the doctrine of incomplete surgery is acceptable, it encourages a liberal attitude toward operation. We are distressed when encountering patients who because of pelvic pain and a diagnosis of salpingitis have had both tubes removed in the age of reproduction. Our experience leads us to believe that regardless of the best intentions of the surgeon who subscribes to such an idea, the results are not good.

Colpotomy. One hundred and sixty-eight patients who had pelvic abscesses were treated by initial colpotomy. This is used only when a fluctuant mass is present in the cul-de-sac and approachable in the midline. It has been our policy to postpone colpotomy from 24 to 48 hours after hospital admission. This allows time to correct dehydration and to establish an antibiotic level using penicillin and streptomycin. Not infrequently the midline pointing of the abscess is not always assurance of its confinement to the cul-de-sac.

An analysis of our records reveals many instances where the easily approached abscess was but a part of much more extensive disease. This has been disclosed in several autopsies as well as in subsequent abdominal operations. In fact, these patients are often so seriously ill as to discourage further surgical treatment. Many of them represent neglected ruptured abscesses.

Colpotomy is still a very worthwhile procedure especially in the younger age group. Even though a high percentage require additional surgical treatment later, colpotomy plus antibiotics may eliminate the necessity for a pelvic laparotomy. Of course, even in the younger age group incapacitating pelvic masses will eventually require pelvic exploration.

Secondary Surgery. The optimum time for following colpotomy with intrapelvic surgery has not been altered appreciably. We prefer

to allow an interval of 6 weeks to 3 months to judge the need.

Johnson, Collins, and Webster[6] reported two patients who became pregnant following colpotomies for a pelvic abscess. No patients in our series became pregnant after colpotomy. Therefore, we feel retention of infected organs has little value in preserving childbearing function.

Primary Definitive Surgery. One hundred and five cases were treated for tubo-ovarian or pelvic abscesses by definitive surgery. The patients with acute exacerbations of pelvic or tubo-ovarian abscesses usually present evidence of general peritonitis, and judgment as to whether there has been a rupture may be severely taxed. However, in the absence of strong evidence to suggest such a catastrophe we follow a conservative pattern. Response is as a rule quite evident within 72 hours, and in about 7 to 10 days the patient is often symptom-free. At this time decision as to further management depends upon age, size of the mass, and a history of previous flare-ups. The younger patients, usually those below 30, are most frequently discharged to be observed, which allows time for further resolution of the pathologic state. Our "all or none" philosophy dictated this policy. In the older group we often proceed with intrapelvic surgery.

Conservative operative treatment or perhaps better to say, incomplete operation has been abandoned almost completely. The incidence of total hysterectomy and bilateral salpingo-oophorectomy is more than 90 per cent. There is some question as to whether this surgical treatment should be postponed after the initial response. It is here that we see some disagreement even among members of our own staff as to the optimum time for operation. Some would postpone operation and allow the patient to "cool off" for approximately three months, feeling that the operation would then be technically more feasible. Others believe that with antibiotics and supportive measures this delay is not necessary.

Acute Rupture of Tubo-Ovarian Abscess

Recent reports, especially that of Vermeeren and TeLinde,[7] have directed attention toward the diagnosis and treatment of the patient with an acutely ruptured tubo-ovarian abscess. It is because of this view, even though this condition has been considered rare, Vermeeren and TeLinde were able to find almost 400 reported cases. Their report divided the patients managed by them into two groups; those treated prior to 1944 without immediate operation, and those treated after 1944 with immediate abdominal exploration. The mortality rate of the first group was 90 per cent and that of the second group 12 per cent. Such a striking reduction is highly significant. Miller[8] called attention to this syndrome and reported 44 cases in 1945. He advocated immediate removal of the affected adnexa and pointed out that the prognosis was generally fatal without immediate operative interference. Lardaro[9] reported that between 1935 and 1951, 11,016 patients were treated for pelvic inflammatory disease at Bellevue Hospital. Seven hundred and fifty-one of these had tubo-ovarian abscesses and 23 were diagnosed as being ruptured. He advocated immediate operation pointing out that one out of 7 operated upon within 12 hours died, whereas 7 out of 12 operated after 12 hours expired. The reports of striking reductions in mortality rates by the use of immediate operation are very convincing. Lowrie and Kron[10] reported an interesting case of a seven months pregnant woman with a ruptured tubo-ovarian abscess. A cesarean hysterectomy was performed and the patient lived.

We are in complete agreement with previous reports advocating immediate operation for the patient with an acutely ruptured tubo-ovarian abscess. It is urged, however, that caution be exercised in making this diagnosis for fear that the door may be opened for surgical treatment of acute pelvic disease which responds so well to conservative therapy. Therefore, we wish to define and limit this emergency operation to the tragic or overwhelming rupture as differentiated from the leaking abscess. These later ones may be the "flare-ups" of old chronic disease. It seems very likely that the old theory of exacerbations being due to reinfection might be superseded by a newer concept based on subacute ruptures of high pressure leaks of pelvic abscesses. Obtaining pus by aspiration of the cul-de-sac is not absolute evidence of a rupture of major proportions as has been implied by other reports. It is our feeling that

some evidence of shock or vasomotor insufficiency differentiates the tragic from the nontragic rupture. It is in the major type of rupture that the mortality has been so high. We do not believe that operation for the lesser types should be done until the opportune time has been reached by careful preparation.

Between 1941 and 1955 a diagnosis of ruptured tubo-ovarian abscess was made on 28 patients on the gynecology teaching service in the City of Memphis Hospitals. The average age of this group was 34.6 years, and the average duration of illness prior to rupture was 23.5 days. Acute abdominal pain was the most common complaint. Nausea and vomiting was the next most frequent. Abdominal tenderness, distention, a palpable mass, and fever were the other prominent signs. Most patients exhibited at one time or another some degree of vasomotor insufficiency such as syncope, sweating, pallor, restlessness, although clinical shock was recorded in only one-fourth of the cases. The usual symptomatology is that of a patient who has a sudden onset or an exacerbation of pain in the lower abdomen. When this is accompanied by most of the other symptoms and signs, such as to suggest general peritonitis along with some manifestation of shock, it is as near to the picture of the syndrome as we can enunciate. That these rigid criteria may cause us to overlook the occasional patient is recognized.

Twelve patients in this series had abdominal surgery. Two of these had immediate operation and both were operated upon during the last year. These 2 patients survived, whereas only 2 of the 10 who had delayed surgical treatment survived. Of the 2 who had immediate operation, one had a bilateral salpingo-oophorectomy and the other an excision of the affected adnexa. Of the 2 who had delayed operation and lived, one had a left salpingo-oophorectomy and the other an exploratory laparotomy and abdominal drainage. Twenty-four patients out of this series of 28 expired giving a mortality rate of 86 per cent.

Summary

A review of the records of 309 patients with tubo-ovarian or pelvic abscesses was made to determine whether an optimum time for surgical intervention could be definitely established.

Three categories are discussed; namely, cul-de-sac abscesses, tubo-ovarian abscesses, and ruptured pelvic abscesses.

The difficulty and hazards associated with the diagnosis of ruptured abscesses is presented.

Immediate operation for the acutely ruptured abscess is urged, but *caution* should be exercised in making the diagnosis.

The optimum time for operation for the nontragic tubo-ovarian abscess with exacerbation is not crystallized.

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Discussion (Abstract)

Dr. John R. Kight, Norfolk, Va. The authors have presented a series of 309 cases of pelvic infection treated surgically. This study was initiated with the idea that the results obtained would in some way indicate a basis for more accurately determining the optimum time for surgical intervention.

In discussing this subject one must remember that such procedures for pelvic infections are in cases that represent a failure of satisfactory response to antibiotic therapy, or those in which antibiotic therapy was not used at a time favorable for the prevention of a pathologic process. Therefore one would be hesitant in adopting a new policy based on the supposed value of antibiotics as a surgical supplement.

We agree with the authors in their indications for colpotomy, using it only when a fluctuant mass is present in the cul-de-sac and approachable in the midline. But once these criteria are fulfilled, we believe *immediate* colpotomy is indicated and cannot concur with their belief that a period of 24 to 48 hours of supportive therapy is advantageous.

Their paper presents an excellent discussion of the problems involved in deciding on the optimum time for primary definitive surgery and for operation secondary to colpotomy. It emphasizes the value of adopting an "all or none" philosophy. A review of the De Paul Hospital records over a 5 year period

shows that we have not altogether followed an "all or none" policy. The results obtained when digressing from such certainly confirms the need for closer adherence. Our view in regard to leaving a questionable or borderline ovary in the younger age group seem to be more lenient than those expressed by the authors. This does not mean approval of incomplete operations such as bilateral salpingectomies, etc., in which the remaining structures are often left without purpose.

Another impression gained from this review was that on those services where an "all or none" policy was followed, a too conservative attitude existed in many cases, delaying operation an unnecessary length of time, thereby subjecting the patient to an unreasonably prolonged illness.

The authors confess they have not found the answer to the optimum time for primary definitive surgery and operation secondary to colpotomy. They admit disagreement even among members of their own staff as to the advisability of continuing with their policy of allowing a "cooling off" period. Our policy in De Paul Hospital has been to continue along the lines of conservative management. We, likewise, have had disagreements and recently had a few cases operated upon with tubo-ovarian and pelvic abscesses immediately following response to medical management. Although these patients have done well, we are still reluctant to accept a policy of immediate operation and will await further evidence of its advantages.

Referring to the discussion on acute rupture of tubo-ovarian abscesses, one can assume that up until the past year, the series of reported cases have been treated by supportive and antibiotic therapy in conjunction with or without delayed operation. The results by this method were most unfavorable and have been reported as such. The authors have had the opportunity of proving to themselves that in this condition a change of policy has been necessary.

For those who continue to question the value of immediate operation as compared with the results that may be obtained with antibiotics in a ruptured pelvic abscess, this paper should serve as a valuable reference.

Doctors Who Signed the Declaration of Independence

In 1776 Josiah Bartlett was 47 years of age, described by his biographer as "a tall man with a fine figure . . . who . . . wore his auburn hair in a queue." He was considerably more than that. He was a distinguished Massachusetts physician and an able and ardent patriot. He already had suffered for his interest in politics; he had been ousted from his post as justice of the peace by the Royal Governor of Massachusetts, and had seen his home burned to the ground.

By 1776 Dr. Bartlett clearly had made his choice. So it was natural that as a Massachusetts delegate to the Continental Congress he signed the Declaration of Independence. Perhaps it was only an accident, but he was the second person to sign the engrossed document at the formal ceremony on August 2 of that year.—(From the A.M.A. Special Report 84-30, 1956.)

Allergy to Meprobamate with Some Observations Regarding the Tranquilizing Drugs*

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The widespread use of the "tranquilizing" drugs makes these observations very timely.

DURING THE DECADE following World War II, the medical profession has been bombarded with an amazing number of new drugs for a myriad of therapeutic uses. As a result the incidence of drug reactions has multiplied rapidly, and in both the general and special medical journals frequent reports of isolated hypersensitive reactions are encountered. Almost any drug may sensitize man and in a variety of clinical patterns. This fact plus the rapid turnover of new drugs puts the busy clinical practitioner at a real disadvantage. For the conscientious physician an untoward side effect becomes an immediate personal problem rather than a distant well-documented statistic. It is for these reasons that the profession should be promptly informed of any unusual reactions to a drug as observed by physicians employing it in every phase of clinical practice.

In the past few years many medications have been introduced with the semantically inoffensive appellation of "tranquilizers," or ataractics, as opposed to the earlier so-called sedatives of the barbiturate and bromide eras. These compounds have been alleged to soothe and calm the tense and harassed patient, bringing about a mood change described by Fabing as "detached serenity," and achieved without undue hypnotic sedation. Up to the present time, however, no pharmacologic test has been developed to which all drugs used as tranquilizers show a specific positive response. In the pre-"tranquilizer" era, these drugs would have been grouped in accordance with some of their other pronounced and useful pharmacologic actions, such as hypnotics, sedatives, spasmolytics, antihistaminics, anticholinergics, muscle relaxants, anticonvulsants, and the like.[1]

One must admit, however, that the "tranquilizers" appear to be evoking a revolutionary effect upon our society,—in the arts and in politics. Such potent weapons are these drugs that they are capable of making normal men apathetic, depressed, lacking in initiative and feeling "isolated from their environment." Medically, they have stimulated new and intensive research in neurophysiology and chemistry, particularly of the brain and its functions. They have advanced the development of psychiatry by contributing to the concept that diseases of the mind are diseases of the brain substance and, as such, can be treated in a similar manner as diseases of any other organ of the body.

Classification of Drugs

Berger has classified the most important tranquilizers into four groups:[1] (Table 1).

1. Compounds derived from phenothiazine,—such as promazine, chloropromazine, promethazine (Phenergan), and ethopropazine (Parsidol).

2. Reserpine and related alkaloids,—these substances liberate serotonin in the brain.

3. Compounds derived from diphenylmethane,—such as azacyclonol (Frenquel), benactyzine (Suavitil), hydroxyzine (Atarax), adiphenine (Trasentine), meclizine (Bonamine), and chlorcyclyzine (Perazil). All these substances have been shown to inhibit the enzymatic breakdown of a variety of drugs.

4. Compounds derived from substituted propanediols,—such as meprobamate (Equanil and Miltown), mephenesin (Tolserol and

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TABLE 1

CLASSIFICATION OF THE TRANQUILIZERS (BERGER)[1]

I. *Autonomic Suppressants*	II. *Central Relaxants*
A. Derived from phenothiazine	A. Substituted propanediols
1. Promazine (Sparine)	1. Meprobamate (Equanil and Miltown)
2. Chlorpromazine (Thorazine)	2. Mephenesin (Tolserol, Mephate)
3. Promethazine (Phenergan)	3. Dimethylane
4. Ethopropazine (Parsidol)	
B. Reserpine and related Alkaloids	
C. Diphenylmethane	
1. Azacyclonol (Frenquel)	
2. Benactyzine (Suavitil)	
3. Hydroxyzine (Atarax)	
4. Adiphenine (Trasentine)	
5. Meclizine (Bonamine)	
6. Chlorcyclyzine (Perazil)	

Mephate), and 2 substituted 4- hydroxymethyl 1, 3 dioxolane (Dimethylane).

The pharmacologic properties of the tranquilizers permit their division into two distinct classes: one group, "autonomic suppressants," comprise the phenothiazine, reserpine, and the diphenylmethane compounds; and the second group, central relaxants, contain the meprobamate, mephenesin, and related compounds (Table 2).

The *autonomic suppressants* show an antagonism to chemicals that regulate certain functions of the autonomic nervous system, such as acetylcholine, histamine, and serotonin; and appear to exert a stimulative effect on the sympathetic hypothalamic centers.

The *central relaxants,* or propanediols, appear to have a selective blocking action on the interneuronal circuits. Few drugs in recent history have gained the wide and rapid acceptance of meprobamate (Equanil and Miltown). Its apparent lack of toxicity and its broad range of usefulness have increased the consumption beyond any predictable magnitude. So great has been the demand for this drug since mid-1955 that there have been appreciable lengths of time when it was not obtainable. Surveys have estimated that two million or more prescriptions per month have been written for it, yet the over-all incidence of reaction is minuscule and a tribute to the careful predistribution investigations of the drug manufacturer.

TABLE 2

DIFFERENCES BETWEEN THE TWO GROUPS OF TRANQUILIZERS

Type of Action	*Autonomic Suppressants*	*Central Relaxants*
Adrenolytic action	present	none
Anticholinergic action	present	none
Antihistaminic action	present	none
Strychnine toxicity	increased	decreased
Hexobarbitone synergism	marked	slight
Conditioned reflexes	depressed	unaffected
EEG changes	generalized	localized (thalamus?)
Convulsive threshold	decreased	increased
Multineuronal reflexes	unaffected	depressed
After discharges	unaffected	decreased
Muscle spasm	unaffected	released

Clinical Study

We have investigated this drug since 1955 following the unfortunate death of Dr. Lowell Selling who did the first studies in our community.[2] We should like to report on the allergic or hypersensitive reactions we have encountered in our patients, plus an analysis of similar untoward reactions by other investigators with controlled groups of diverse ages and illnesses.[3-6]

None of the reactions has been fatal and all have been reversible. We have had 8 allergic reactions in approximately 145 patients treated, a higher over-all incidence than has been reported probably because of the greater number of patients with an allergic background and constitution. The type of reactions encountered have been similar, in general, to those reported by other investigators and may be classified as follows:

1. Dermatologic manifestations. (73%)
   a. Pruritus, with and without urticaria. (41%)
   b. Exanthematic eruptions, morbilliform in type, usually involving the trunk and lower extremities. (37%)
   c. Purpura simplex with and without thrombocytopenia. (22%)
2. Systematic patterns. (16%)
   a. A pattern of serum sickness associated with fever 102-105° F., generally accompanied by skin manifestations as noted previously, and arthralgias in about one-third of the cases. In one instance there was possible cardiac involvement with development of transient atrial flutter-fibrillation arrhythmia. In several instances bronchospasm occurred in those patients in whom fever and angio-edema were more severe. Transient albuminuria was noted in two instances. No liver involvement has been noted clinically in any patient.

Interestingly a good number of patients developed an "immediate" reaction, as early as two hours after the ingestion of their first meprobamate tablet. In these instances we tried to ascertain whether they had ever been given related compounds such as mephenesin, but this was never demonstrated. Several of our patients with reactions had a previous history of drug sensitivity to such medications as sulfonamides, penicillin, and aspirin.

Usually our patients developed allergic responses after they had been on the drug from one to three weeks. In all cases reactions cleared within one to three days upon withholding the drug and by use of antihistamines, calcium gluconate intravenously, and the corticoids. Subsequent use of this drug, after a rest interval of one to two months, usually resulted in a more systemic and more severe response. In two instances of mild urticaria the patients used the drug again after two months and were able to tolerate it for short intervals only.

Gastrointestinal reactions manifested by mild nausea to severe vomiting, and occasional diarrhea, were reported in 13 cases. Since there were no other reactions in any of these it is our feeling that these probably constitute a local tissue irritation from the drug itself.

Miscellaneous responses such as convulsions, "shock organ response" as in "flare-ups" of the skin lesions of lupus erythematosus, old joint pains, vague mental excitement or even "fogginess," also may be side reactions or pharmacologic responses of diseased tissues.

Skin tests by the scratch method with meprobamate, gelatin starch, magnesium stearate, and alginic acid (the ingredients of the tablets), yielded negative reactions in all cases. Passive transfer serum tests in four instances also gave negative responses.

A few representative case reports may illustrate these reactions more dramatically.

Case 1. D. C., female nurse, age 37, had her first drug reaction in 1941 when she was given sulfanilamide and, after 24 hours, developed high fever and severe hematuria. Eight years later she was given sulfamerazine; after only the first two pills she developed hematuria. In December, 1955, the patient tried a Miltown tablet of 400 mg. to "relax" her. Four hours later she developed severe itching with generalized urticaria, and chills with an elevation of temperature to 105° F. These disappeared in twenty-four hours following calcium gluconate with added chlortrimeton intravenously, and ACTH gel, 40 units, intramuscularly. Two weeks later, not convinced that the previous reaction was due to the drug, the patient again took a 400 mg. tablet meprobamate. Within 3 hours there was a recurrence of high fever, chills, and beginning urticaria. Prompt repetition of the previous treatment produced improvement within 8 hours.

Case 2. Mr. B. P., age 48 years, gave a history of severe viral respiratory infection several weeks previously, and a resistant hacking cough. He was given Miltown since he was nervous and tense, trying to carry on a heavy business schedule. Two weeks later the patient developed a maculopapular rash over trunk and back, and had chills and fever of 102.4°F. At first a contagious disease had to be differentiated in diagnosis since there were numerous cases of rubella among the children in the community. The blood culture was negative; there was a white cell count of 9,000 with moderate polynucleosis. Miltown was discontinued, and within 48 hours the rash had cleared and the patient was afebrile.

Case 3. Mr. R. G. C., age 55 years, an executive, was induced by a friend to take some "happy" pills while on a 250 mile trip to visit his daughter. One hour after taking a 400 mg. meprobamate tablet, he developed a fine rash in the axillas, lower arms, and groin areas without itching. On the fourth hour he took another tablet, and on the sixth hour developed severe chills and a fever of 102.8° F., with a marked diffuse macular and petechial rash, and a rapid irregular heart rhythm. A recent complete insurance checkup for a life insurance policy had shown him to be in excellent health. The patient admitted noting recently occasional "skipped beats" when excited. He had a nasal operation for sinus blockage in 1925.

Laboratory tests showed the sedimentation rate to be 12 mm. per hour, a white cell count of 11,000 with 19% stabs, 63% segmentors, 11% lymphocytes, and 7% eosinophiles. Two days later the white count was 11,500 with 15% stabs, 45% segmentors, 23% lymphocytes, and 17% eosinophiles. PBI was 2.5 mgc. and serum cholesterol 230 mg. per 100 cc. Chest x-ray study was normal.

The patient was afebrile after 36 hours and by the third day the rash had subsided except for a slight bluish petechial discoloration. The blood pressure, which had fallen to 98/70 on admission, was 120/80 on the fifth day, with regular sinus rhythm and no evidence of myocardial damage on ECG.[7]

Case 4. A woman who had lupus erythematosus developed numerous new lesions typical of her disease, along with "fogginess" of the mind and difficulty in locomotion. No untoward effects were noted in the blood or urine examinations.

Discussion

At a recent conference on meprobamate held at the New York Academy of Sciences,[4] reports from scattered areas of the country on controlled groups of patients in hospital clinics and in private practice revealed that 25 of 2,395 patients experienced some form of untoward reactions, an over-all incidence of 1

per cent. One hundred and forty-four children from six months to 16 years of age, with diagnosis of mental disturbance, pre-psychotic states, cerebral palsy, or basal ganglia lesions, had been taking meprobamate for two to six months with only one reported instance of prolonged vomiting, and another of prolonged convulsions in the cerebral palsy group, requiring discontinuance of the drug.

The majority of reactions to drugs used in therapy fall into definite clinical patterns, and the mechanisms have been lucidly discussed in a recent monograph by Alexander.[8]

In the cases of meprobamate sensitivity reported elsewhere and in those observed personally the hypersensitivity reactions also seem to follow a definite clinical response, locally involving mainly the skin, and systematically presenting the pattern of "serum sickness." Since the predominant actions of the tranquilizers are in the vital centers regulating the body's physiologic and chemical reactions, the differentiation of hypersensitivity reactions from side effects, individual idiosyncrasies, and even untoward pharmacologic responses by altered tissues may at times be fraught with great difficulty. It does seem advisable, however, to make the profession more alert to the complications, if not the genuine hazards of sensitization, so that it may be looked for and not confused with some other disease process. A sudden rise in temperature with chills during convalescence following an operation, or during recovery from an infection, may present a formidable problem. For these reasons it seems timely to call attention to this complication of therapy, especially with one of the newer of the tranquilizers, meprobamate, which has reached such a prominent place in everyday office and institutional practice.

Summary

1. A newer grouping of the tranquilizers, their possible modes of action, and their significance medically and socially has been discussed.

2. An "allergic" clinical pattern of reaction to the meprobamates has been described, with an over-all incidence of 1 per cent in collected studies.[4] All of the reactions were completely reversible and generally mild.

3. Hypersensitivity to new drugs should be reported promptly, so that the medical profession can be made aware of the developing "reaction-patterns."

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Discussion (Abstract)

Dr. Warren J. Raymer, Houston, Tex. The paper by Drs. Klotz and Bernstein reminds us that we must be constantly on the alert for toxic and sensitivity reactions to drugs, especially new ones.

The authors have reviewed presently available data concerning adverse reactions to these drugs. Evidently, reactions to the tranquilizing drugs vary from paradoxical excitement and agitation to confusion, and may include gastrointestinal symptoms, skin involvement and other phenomena.

Apparently, chlorpromazine (Thorazine) heads the list of tranquilizing drugs in producing adverse reactions. My experience with this preparation includes two cases of contact dermatitis and one of nonthrombocytopenic purpura. Urticarial lesions caused by oral administration of Thorazine in one case were of a fixed type, rather than the usual migratory eruption ordinarily expected in urticaria.

I have seen only two patients who have demonstrated reactions to meprobamate. One of these patients suffered a generalized erythematous dermatitis occurring within thirty minutes after taking his first tablet. The other was a nurse who took a tablet "just to see what sensation she would experience." She developed an urticarial reaction shortly afterward which persisted for three days. Further questioning revealed that she had taken one-half tablet several months earlier with a milder, but similar response.

I would also like to emphasize that patients frequently exhibit reactions to Equanil or Miltown with the first dose. This is contrary to our idea that a previous sensitizing dose is necessary.

A central agency or committee to which we could report our individual experiences of sensitivity reactions to drugs would be worthwhile. Many physicians do not have the time to publish their observations, but probably would report drug reactions if they had a simplified form on which they could note their findings. A statistical evaluation would ultimately be available.

Again I wish to thank Drs. Klotz and Bernstein for bringing these observations to our attention.

Dehydration for the Common Cold*

GUY T. VISE, M.D., *Meridian, Miss.*

These are interesting thoughts which should stimulate further controlled investigation.

FOR THE PAST FIVE YEARS, dehydration has proved of great value to me in treating the common cold. Previously, forcing fluids had been the recommended procedure in treating the common cold. Sometimes a complete reversal, or about-face is necessary in medical practice, such as early ambulation versus bedrest for surgical and obstetrical patients. Dehydration is a complete reversal in our therapy of the common cold and it usually produces spectacular results. One old joke told us by our professors was, "Treat a cold and it will get well in 14 days; leave it alone and it will get well in two weeks." This is an admission of the ineffectiveness of our therapy in many cases.

Dehydration

First Case of Dehydration. The first patient to provoke this idea of dehydration for the common cold was a 22 year old lady teaching in our city schools and had a head cold for 4 months, with blockage of her nasal passages. The edema and congestion was great and all other treatment had failed. Dehydration was begun as for cardiac insufficiency by limiting fluids to 1,000 cc. daily and by restricting the salt intake. Within 48 hours she had the greatest relief she had had in the four months. The nasal mucosa lost its edema and a cure was effected.

This idea of dehydration for the common cold was fascinating and it was tried in other cases with rapid improvement. Several methods of dehydration have been used and all have been more or less effective. It was necessary to work out standards for evaluating results. The common cold is a variable disease and may vary from a severe infection to allergic rhinitis.[1-4] End results of therapy are necessarily of a subjective nature and so results were classified as poor, good and excellent.

Tests for Dehydration. Tests to determine the effectiveness of therapy, or the degree of dehydration, were needed. A rapid weight loss in a few hours largely represents the amount of fluids removed from the body. The average loss in weight which produced effective symptomatic results was 2 to 4 pounds for an adult, or roughly, 2 to 3 per cent of the body weight. The other test to determine the effectiveness of dehydration is an increase in the specific gravity of the urine. A concentration of 1.020 or above indicates good results in most instances. Conversely, a low specific gravity indicates (usually) that the patient is over-hydrated, and a gravity of 1.010 or less is an indication for dehydration. The color of the urine may indicate its concentration; the patient may be advised that he must limit his fluid intake to produce a darker color of the urine.

Rationale of Dehydration. The theory, or rationale, of dehydration for the common cold is that the mucous membranes and tissues of the upper respiratory tract shrink as congestion is relieved. There is more adequate circulation which is essential for healing. The pain and discomfort of a partial vacuum in any of the numerous sinuses is relieved when the mucous membrane at the ostium shrinks and permits the exchange of air in the previously blocked sinus. With more adequate circulation in the diseased tissue, chemotherapy or antibiotics are more effective.

The use of a laxative aids dehydration. Diaphoresis, or sweating, is a very rapid and effective method for dehydration.

Most of the patients treated by dehydration have been office patients who were ambulatory; many others were ill enough for hospital care. The response in most cases was excellent.

Regardless of the cause of the common cold, we can reverse one of the fundamental pathologic processes of the common cold by dehydration. Local shrinkage and dehydration, by

*Chairman's Address, read before the Section on General Practice, Southern Medical Association, Fiftieth Annual Meeting, Washington, D. C., November 12-15, 1956.

the use of nasal drops, sprays and inhalers, has been widely accepted and is beneficial. Beneficial effect of local dehydration should be augmented by systemic dehydration and not counteracted by over-hydration by forcing fluids.[3,5]

Physiologic Considerations

Weather and Climate. I have been able to correlate the physiology of the common cold and the rationale of dehydration with some climatic conditions. The weather has been incriminated as a cause of the common cold for over 2,000 years.[6] This appears to be true. We are literally living in a sea of air[7] which varies widely in temperature, barometric pressure and water content (or relative humidity). During cold, dry weather the loss of water from the body as vapor in the breath is easily visible. Without an adequate intake of fluids, the body becomes dehydrated. During periods of very high relative humidity (air saturated with water vapor), the reverse occurs, and the body becomes over-hydrated, producing stuffiness of the head and nose, increased weight, swelling of joints (noticed by arthritics) and generalized edema. Wet or damp weather predisposes to colds as does living in a basement apartment or any damp place. Cardiac patients seem to suffer more in damp weather. During dehydration therapy several patients gained 2 or 3 pounds in body weight within 24 hours when there was a change in the weather accompanied by a very high relative humidity. The 2 to 3 pounds gain in weight was evidently from water absorbed through the mucous membranes of the air passages and through the lungs. (This year's newspaper account of a car accident victim living 9 days pinned under a car in a wet, mountainous terrain affirms the theory that a human body literally "drinks" up water if the humidity is high.)

Physiology of Breathing. Let us analyze the physiology of breathing. The mucous membranes of the nose, throat and pharynx raise the temperature of inspired air to 86° F. and the relative humidity to almost 100 per cent.[8] The remaining elevation of the air temperature takes place in the lungs. This "conditioning" of air for the lungs requires rapid work by the mucous membranes and a rapid adjustment when there are changes in the atmosphere or in the body requirements. If the air is cold and dry it must be warmed and wetted rapidly. Thus the nose may be wet and dripping if it is a healthy well-functioning nose of an athlete on a cold dry day. On a hot wet day the mucous membranes have little work to do. On a cold, wet day no moisture is needed, but the mucous membranes are congested and swollen in the attempt to warm the air.

Allergy. Allergens cause edema of the nasal mucosa with impaired function leading to infection. Unfavorable weather plus allergens create a heavy load for the mucous membrane, which, if it is too heavy, may result in hay-fever and asthma.

Pathologic Changes of the Common Cold. As an end result of stress factors, whether caused by allergens, by weather, by infection or by vasomotor changes, the mucous membrane of the upper respiratory passages becomes swollen and edematous, the air passages are narrowed and the openings to sinuses and accessory organs are either partially or completely occluded. All of this predisposes to various stages of infection, from (1), a local inflammation with redness of the nose and throat, to (2) sinusitis of varying degree with blocking of the ostia producing the typical "vacuum" headaches, on to (3) purulent infection of the sinuses, or (4) purulent otitis media, or (5) bronchopneumonia.

Treatment

Cure or prevention of this sequence of pathologic processes requires (1) reversal of the edema, (2) prevention of infection, or its further progression, and (3) putting the injured tissues at rest.

Routine Treatment of the Common Cold. The following routine has been found satisfactory for dehydration therapy of the common cold:

1. Foods and fluids are limited to one cupful of soup, fruit juice, vegetable juice, tea, coffee or a fruit every 3 hours while awake. No water is permitted and very little, or no salt.
2. A saline laxative is given.
3. Penicillin 600,000 units and/or tetracycline 250 mg. are given every 4 hours.
4. Aspirin gr. X p.r.n.
5. Codeine gr. ss p.r.n.
6. Antihistamines, using Benadryl if sleep is desired.
7. Hot sweat pack for 2 hours once daily.

Hot Sweat Pack. An infected or injured mucous membrane cannot function properly.

If put at rest temporarily, it heals quicker. To create a state of rest for the nasal mucosa I have used "the hot sweat pack." With the relative humidity almost 100 per cent under the cover in a hot sweat pack, the air is similar to the air in the lungs and requires no moistening or raising of the temperature to that of the body by the mucous membranes of the nose, throat, pharynx, larynx or trachea. Furthermore, excessive fluids are being removed through perspiration. Nature ultimately would accomplish this by a high fever and perspiration if the infectious stage progressed fully to a streptococcal sore throat or to a bronchopneumonia.

Advantages of using the hot sweat pack to aid in dehydration for the common cold are:

1. The patient is at rest and may go to sleep.
2. Dehydration is accomplished by perspiration.
3. The body temperature is increased, which may increase the defense mechanisms.
4. The mucosa of the nose and throat is put at physiologic rest and does not need to add water or humidity to the inspired air, nor to raise the temperature to that of the body since the patient is:
   (a) Rebreathing air that is at body temperature.
   (b) Rebreathing air that is already at 100 per cent humidity, this humidity being obtained from the lungs and not added from an outside source.
5. Congestion of the nose and throat rapidly subsides permitting:
   (a) Freer passage of air into the lungs,
   (b) Circulation to return to normal, and
   (c) Antibiotics or chemotherapy to reach the infected areas for rapid healing.

Technic of giving a hot sweat pack:

1. Thirty minutes before treatment give:
   Aspirin gr. X
   Codeine gr. ss
   Benadryl 50 mg.
2. One minute before treatment, give 2 glasses of *hot* lemonade.
3. Place a cotton blanket under the patient to absorb profuse perspiration.
4. Have patient wear heavy pajamas and socks on the feet.
5. Apply hot water bottles or an electric pad to induce rapid perspiration.
6. Have patient lie on his side to afford an air chamber under the cover.
7. Cover the body entirely, including face and head, with a sheet and two or more blankets.
8. Reassure the patient that he will not smother nor become asphyxiated, and to remain quiet and to sleep if possible, for one to two hours.
9. After one to two hours, dry the skin thoroughly, dress and move to a dry bed.

Other Methods of Dehydration. Other methods of dehydration have been used. The limitation of the intake of salt and sugar is important. Fluids should be limited to 1,000 cc. daily. Intravenous mercurial diuretics have been used; Neohydrin, orally, has been used with good results.

Summary

Several hundred patients having the common cold have been treated by dehydration instead of forcing fluids during the past five years. Good or excellent results have been obtained in nearly all cases. There were some cases in which dehydration proved of little, or no benefit. At the present time it appears that patients having hypothyroidism respond poorly. During the first years of dehydration therapy, only symptomatic results were observed and recorded.

In a series of 41 patients in whom the weight loss and increased concentration of the urine were recorded, the following results were found:

Poor results (symptomatic)	7.3	per cent
Good or excellent results (symptomatic)	92.7	per cent
Average weight loss	2.7	pounds
Average specific gravity of urine increased	0.011	Gm.
Average days treated	2.9	days

Conclusions

The forcing of fluids should be abandoned and a more physiologic approach should be used in treating the common cold.

Patients with frequent colds may be in a state of chronic over-hydration.

Dehydration reverses one of the pathologic processes of the common cold.

The effectiveness of dehydration can be measured by rapid weight loss and by an increase in urinary specific gravity.

Dehydration, by the hot sweat pack technic, affords physiologic rest for the congested mucous membranes of the nose and throat.

Intractable "vacuum" type sinus headaches respond to dehydration.

Weather as a cause or contributing factor to the common cold is a reasonable conclusion.

Patients may absorb water through the mucous membranes of the nose and throat

and through the lungs in damp wet atmosphere.

Over 90 per cent of patients having the common cold reported good or excellent results from dehydration.

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Discussion (Abstract)

Dr. Stanley A. Hill, Corinth, Miss. Dr. Vise has outlined a treatment regimen which will certainly impress the patient that a cold is a serious disease. It will henceforth be counted in the category of severity with gastric resection and advanced cardiac decompensation. Recount the seven steps in the treatment recommended and one will realize that the patient will surely know he is sick! If I were to offer constructive criticism of Dr. Vise's plan, it would be the lack of control. Had he employed dehydration alone without the six other parts in the treatment, there could have been direct evaluation.

The doctor must work with what is available. There are two known facts regarding the common cold that are of practical importance. These are, first, the diagnosis and, second, methods of treating the complicating bacterial infections. Therefore, with present-day knowledge, the practical therapy of the common cold resolves itself, after making the diagnosis, into the prevention of, and attack upon the complicating secondary infections. The surgeon has taught us how to establish the diagnosis. In contrast to the meticulous time consuming method of the internal medicine diagnostician, the surgeon reaches the answer quickly by asking the patient!

When the answer is "yes," rest and drug therapy are begun. Medication is selected to either attack or prevent the secondary bacterial infection. Give an ounce of magnesium sulfate for its time honored and efficacious systemic dehydration. In the uncomplicated stage I like to employ an antihistaminic compound such as Dasikon (Massengill) or Coricidin (Schering). To be effective this must be begun with the first symptoms. In the second twenty-four hours if there has been no improvement, penicillin should be administered in 300,000 units daily doses intramuscularly. If another twenty-four hours elapses without improvement, add Terramycin in 250 mg. doses orally every four hours. There are few upper respiratory infections that will not yield to this four-way cross-fire attack.

This challenging problem would be attacked more appropriately with the establishment of a research team in the South. With sufficient funds which would provide laboratory and clerical facilities, dehydration could be properly evaluated.

Doctors in Public Life

Four physician members sat in the Second Continental Congress in 1775. The next year the Colonies sent eight doctors to the deliberations. In the critical years of 1783-84, eleven doctors were in the young Congresses that struggled to keep the states united. It is a tribute to the versatility of the profession that in the 181 years since 1775 doctors have set in every Congress.— (From the A.M.A. Special Report 84-30, 1956.)

Roentgen Manifestations of Sickle Cell Disease*

DAVID S. CARROLL, M.D.,† *Memphis, Tenn.*

The systemic disease known as sickle cell disease is protean in nature. Among the interesting clinical manifestations are the radiologic abnormalities.

SICKLE CELL DISEASE is a condition of great social and economic importance because sickle cell anemia is more common in the negro race than all other primary blood dyscrasias combined. During the past decade we have had the opportunity of seeing rather complete roentgen examinations on 124 cases of sickle cell disease, and this series forms the basis for this report.

Physiologic Considerations

Sickle cell hemoglobin is an abnormal type of hemoglobin which is less soluble than normal adult hemoglobin when in the deoxygenated state. Under conditions of hypoxia hemoglobin precipitates out in long crystals which distort the erythrocytes into bizarre elongated and pointed shapes. The percentage of the abnormal hemoglobin in the erythrocytes is a function of the hereditary factors involved in the individual case. If the abnormality is inherited from one parent only, the cells will contain from 20 to 40 per cent abnormal hemoglobin and from 60 to 80 per cent normal hemoglobin. These individuals are said to have the sickle cell trait, which is a relatively benign condition and compatible with a fairly normal life expectancy. Approximately 8 per cent of the negro population of this country have the sickle cell trait. However, those individuals who inherit the abnormality from both parents have no normal hemoglobin, and all of the hemoglobin of the red cells is the relatively insoluble sickle cell type. For every 40 patients with sickle cell trait, there is one patient with sickle cell anemia.

An erythrocyte containing sickle cell hemoglobin has a much shorter life expectancy than does a normal erythrocyte. As a result, patients with sickle cell disease are chronically anemic and, in many individuals, this anemia is the most severe and protracted anemia encountered in medicine. As a result of the severe protracted anemia, there is a marked hyperplasia of the bone marrow in an effort to compensate.

Any condition of local hypoxia of the tissues will result in precipitation of sickle cell hemoglobin. The result is that the erythrocytes assume an elongated bizarre rigid shape. These abnormal erythrocytes have difficulty in getting through capillaries and therefore stasis of blood occurs. This stasis further increases the degree of hypoxia and a vicious cycle results. The local hypoxia produces damage to the blood vessel walls and, if they are rather severely injured, perivascular exudates and hemorrhages occur. Clot activating substances are liberated and this initiates the coagulation of blood with the formation of intravascular thrombi. Thrombosis, of course, leads to infarction, necrosis and fibrous tissue scarring. These thrombotic phenomena may occur in any tissue or organ in the body.

Symptomatology

Sir William Osler once called syphilis "the great imitator." If syphilis is the great imitator of other diseases, sickle cell disease certainly runs it a close second. The symptomatology may be referable to any organ in the body. Anemia, although mild in some cases, may be extremely severe, and this anemia, of course, produces the usual symptoms of weakness and malaise. Characteristically, the disease manifests itself in crises, during which there is fever and leukocytosis, along with marked exacer-

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bation of other symptoms. These crises are to be expected when one considers the fact that hypoxia produces sickling, and sickling produces hypoxia. This vicious cycle, when initiated in the body as a whole, produces marked exacerbation of symptoms together with fever and leukocytosis. During such periods there is a marked destruction of erythrocytes, and as a result there is an hemolytic jaundice which may be rather severe.

Probably the most characteristic single symptom of sickle cell disease is a rheumatic type of pain in bones and joints. Pain in bone and joints, fever and leukocytosis may easily lead to an erroneous provisional diagnosis of rheumatic fever. Backache may be rather severe in some patients and we have encountered an occasional case in which the initial clinical diagnosis was ruptured intervertebral disc. One of the most confusing symptoms that patients with sickle cell disease often show is abdominal pain; these abdominal crises may mimic an acute surgical abdomen. Obliterative vascular phenomena in the legs may lead to severe chronic leg ulcers, and this is the chief complaint of many patients. Cardiac insufficiency is common. If the thrombosis involve the central nervous system, such symptoms as headache, convulsions, pareses and paralysis may be encountered.

Radiologic Changes in Bones

Basically, the roentgen changes observed in bone are due to two fundamental processes. The first is that of marrow hyperplasia, which is an effort on the part of the body to compensate for the severe protracted anemia. This is most evident in flat bones. The second fundamental process is that of a thrombotic phenomenon, which is predominant in long bones. Hyperplastic bone marrow is manifested by decalcification of bone, thinning of the cortex, and widening of the medullary cavity, with or without coarsening of the bone architecture. These changes of hyperplastic marrow in the long bones were seen in only 4 of the 124 cases of sickle cell disease, and all of these patients were quite young. Definite changes due to thromboses in bone were encountered in about 50 per cent of cases. The general reaction of a long bone to hypoxia is that of thickening of the cortex, narrowing of the medullary cavity, and frequently a rather bizarre coarsening of the bony architecture. This is quite commonly seen in sickle cell disease. In addition to this, localized areas of thrombosis, which may be single or multiple, and which may vary considerably in size are evident in many patients with sickle cell disease (Fig. 1, A). Thromboses may appear as a bizarre radiolucent area when the necrosed portion of bone is replaced by hyaline or fibrous tissue (Fig. 1, B). More commonly, however, the thrombotic area is quite densely calcified.

Rather frequently the thrombosis and aseptic necrosis involves an entire ossification center such as an epiphysis. We have encountered 9 cases of aseptic necrosis of the capital femoral epiphysis among our patients with sickle cell disease, and these patients all demonstrated the usual symptoms, physical findings, and roentgen changes of Legg-Perthea's disease (Fig. 2). One patient had aseptic necrosis of the head of the humerus (Haas's disease), one had aseptic necrosis of the primary centers of ossification for the bodies of the ninth and tenth thoracic vertebra,

FIG. 1

A B

(A) Thickening of cortex with narrowing of medullary canal in midshaft of fibula. Bizarre coarsening of bone architecture in upper portion of tibia, in a patient with sickle cell disease. (B) Irregular area of decalcification following thrombosis in lower tibia due to sickle cell disease.

FIG. 2

Aseptic necrosis of capital femoral epiphysis on left in a patient with sickle cell disease.

(Calves' disease), and one aseptic necrosis of the patella (Sinding-Larsen-Johanssen's disease). Since the incidence of epiphysitis or aseptic necrosis in sickle cell disease is so high, —10 per cent of our cases,—it is probably wise to exclude sickle cell disease in all such negro patients.

Seven cases of the series have shown the typical syndrome of sickle cell dactylitis. This syndrome clinically is characterized by painful swelling of the hands and feet, which usually lasts for a period of several weeks and then slowly regresses back to normal. The radiologic findings in sickle cell dactylitis consist of periosteal proliferation about the shafts of some of the metatarsal, metacarpal, or phalangeal bones. In all 7 patients there was involvement of several of these small bones, but in no case did all of the metacarpals or metatarsals become involved. In addition to the periosteal proliferation, cyst-like areas of destruction appear in the involved bones, giving the bone a somewhat honeycombed appearance. All 7 of the cases of sickle cell dactylitis were in children. It is interesting that the roentgen findings lag behind the clinical findings by at least 2 to 3 weeks. The changes apparently are not due to an infectious process because the bones slowly regress to normal, the patients do not have a febrile course as a rule, and broad spectrum antibiotics do not alter the course of the disease. Children with sickle cell disease occasionally show periosteal proliferation about the shafts of other long bones.

Four of our patients with sickle cell disease have had an associated salmonella osteomyelitis. The reason for this increased incidence of salmonella osteomyelitis in patients with sickle cell disease is not definitely known, but it could possibly be due to thromboses in the wall of the gut allowing enteric organisms to enter the blood stream. All of the patients with salmonella osteomyelitis have shown involvement of multiple bones and the infection has been quite severe. Periosteal proliferation

FIG. 3

Salmonella osteomyelitis of left humerus associated with sickle cell disease.

is the first sign and this is rapidly followed by widespread areas of bone destruction, extending throughout the shaft of the bone. Destruction is sometimes severe enough to be associated with pathologic fractures. In none of our cases has the infection crossed the epiphyseal line. Cortical fissuring is frequently seen and it is thought that this is due to the fact that in sickle cell anemia, the Haversian canals are quite wide and permit easy extension of the infection into the cortex of the bone. The combination of rapidly destructive osteomyelitis involving several bones, together with cortical fissuring, is such a typical clinical picture in a negro patient that one should suspect the combination of salmonella osteomyelitis and sickle cell disease (Fig. 3).

Films of the spine and pelvis, in contrast to examinations of the long bones, usually show changes due to hyperplastic bone marrow and not changes due to obliterative vascular phenomena. These changes consist of decalcification of bone and a rather remarkable coarsening of bone architecture. If one cuts across a vertebral body of such a patient at autopsy, the bone cuts with remarkable ease, the cut surface bulges up, and is quite purple in color, being extremely hyperplastic. Such a bone obviously has considerably less structural strength than normal, and it is therefore not surprising that about 30 per cent of our cases have shown definite biconcavity of the vertebral bodies.

FIG. 4

Multiple punched-out lesions of the skull in a patient with sickle cell disease.

FIG. 5

Extreme thickening of the calvarium with perpendicular striation due to sickle cell disease.

Nine of the 124 cases have demonstrated changes in the ribs, vertebrae, and pelvis, which were quite similar to diffuse osteoblastic metastases. These multiple small overcalcified areas are due to obliterative vascular changes. In an older patient such lesions might well cause one to suspect carcinoma of the prostate. However, most of the cases have been in young adults and sickle cell disease was the better possibility.

Other Radiologic Changes

X-ray manifestations of sickle cell disease in the skull are sometimes quite dramatic. The most common finding of sickle cell disease in the skull is simply an increase in the prominence of the diploic markings. These are usually best seen in the posterior parietal areas. Thickening of the calvarium was noted in 20 cases. This is most common in the frontal region but may involve any or all of the calvarium. Nine patients showed multiple round areas of decalcification which resembled the punched out lesions of multiple myeloma to a rather remarkable degree (Fig. 4). These lesions were thought to represent areas of fibrosis and hyalinization following thrombosis. In 7 of the patients there was a rather marked increase in the thickness of the calvarium, with perpendicular striation giving a remarkable "hair on end" appearance (Fig. 5).

It is interesting to note that 9 of the 124 patients showed definite enlargement of the spleen. However, these patients were all young children. With the passage of time thromboses, followed by fibrous tissue replacement, occur repeatedly in the spleen, with only a scarred remnant remaining. It is also interesting to note that 5 patients, in the series of 124, had calcified gall stones. This is not surprising since destruction of large numbers of red cells during crises produce hemolytic jaundice, thereby increasing the likelihood of cholelithiasis. This increase in the incidence of cholelithiasis is more significant when one realizes that the vast majority of the patients were young adults or children, and that very few cases over 30 years of age were seen.

Cardiac enlargement is the most common single roentgen finding in sickle cell disease, although the degree of enlargement is quite variable. There are three possible explanations for the cardiac enlargement. First, the cardiomegaly may be the response of the cardiovascular system to a severe, protracted anemia. Secondly, thromboses occur in the myocardium just as they do elsewhere in the body, and this certainly plays a definite role in the production of cardiomegaly in many patients. Thirdly, the enlargement of the heart can rarely be due to cor pulmonale resulting from repeated widespread pulmonary infarction. Changes in the lungs are usually not remarkable and it is seldom that thromboses are evident on roentgenographic studies. Congestive changes, of course, do occur when the heart is decompensated. Also, we have seen 3 patients with definite acute pulmonary edema, occurring during crises. In one instance the patient died during the crisis, and autopsy revealed a very severe pulmonary edema, the alveoli being filled with sickled erythrocytes.

Conclusion

Sickle cell disease is so protean in its manifestations and resembles other clinical conditions to such a remarkable degree that differential diagnosis is oftentimes quite difficult. The diagnosis is obviously made by hematologic studies. However, it is not uncommon for the roentgen changes to give the first clue as to the true diagnosis.

Definitive Diagnosis and Treatment of Headache*

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The importance of the stress and strain of life in the pathogenesis of headache is not to be disregarded, in fact in most instances is probably the major factor.

"ALL ROADS LEAD TO ROME." Nothing demonstrates this so clearly and vividly as the many varied technics and medications proposed for the treatment of headache. Most of these propositions are the result of sincere and painstaking work, based on experimental and clinical evaluation. Why then, do we continue to approach this problem by so many different routes? Headache is such a common symptom that if one wishes, one can classify it under so many different causes one becomes completely lost.

We have not come here today to confuse the issue but to discuss the headache problem as simply as possible. We find the simple, straightforward approach to the patient is usually the best and most effective. It makes no difference what type of headache it is, or what the accompanying symptoms may be, one has only one head and there are only so many tissues in that head that can produce pain.

Pathophysiology

It will serve our purpose at this time to present a simple explanation of the pathophysiology involved in production of head-pain, although these facts have been clearly worked out and can be presented in a simple manner, there is much more to the problem than this. We must give credit for most of this work to Harold G. Wolff, of New York (Fig. 1 and Table 1). Further work reveals there is more to the problem than the simple presentation of pathophysiology; indeed there are many unanswered facts in this connection. For example, there is often retention of water and electrolytes preceding headaches, and a diuresis following the headache. Although this is a

FIG. 1

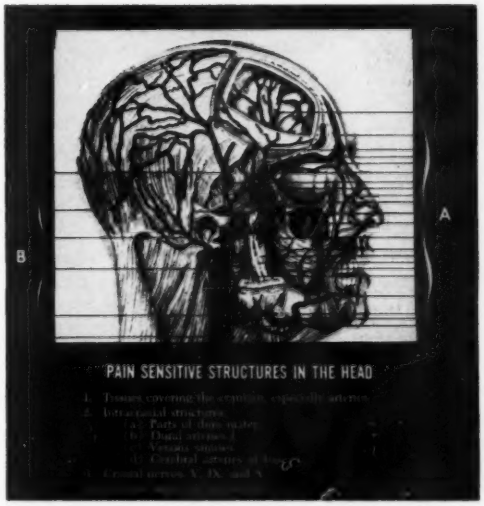

Illustration of the pain structures of the head.

TABLE 1

THE SIX BASIC MECHANISMS BY WHICH HEADACHE MAY ARISE FROM INTRACRANIAL SOURCES

1. Traction and displacement of the longitudinal sinus and contributing veins.
2. Traction of the middle meningeal arteries.
3. Traction of the arteries of the circle of Willis and its branches.
4. Direct pressure on cranial nerves five, nine, and ten, and the upper three cervical nerves.
5. Inflammation in or about any of these structures.
6. Distention and dilatation of intracranial arteries.

EXTRACRANIAL SOURCES OF HEADACHE

1. Headache may arise from distention of arteries, chiefly branches of the external carotid.
2. From contraction and spasm of muscles of the scalp and neck. This latter mechanism may be associated with postural strain, reflexes from pain-sensitive nasal, paranasal and ocular structures, and especially with tension-anxiety states.

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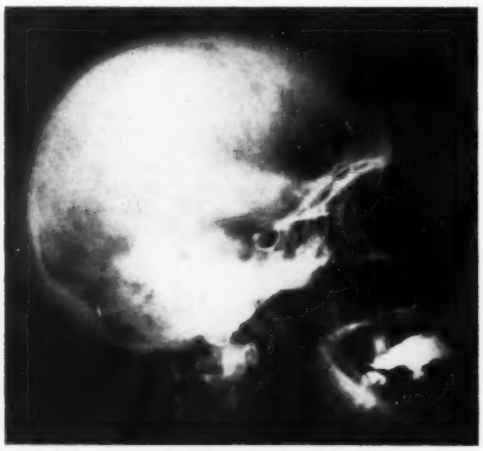
clear-cut demonstration of what happens during a headache it will take on many different forms in the individual patient. Thus if we try to "pinpoint" in each patient exactly what happens physiologically during a headache we shall continue to meet with frustration. A complete understanding of all the facts will help us to understand an individual's headache and give us clues as to treatment. It is not necessary nor possibly advisable to make an exact diagnosis in each case. There is no substitute for a complete understanding of the patients and his problems, and an understanding what the head-pain is expressing physically and emotionally.

Therefore, to get back to the patient sitting at your desk in your office,—how do you handle the problem? As with any other diagnostic problem one must begin with a detailed history, and a physical and laboratory examination. Thereby one can eliminate specific instances of brain tumor, eye, ear, nose, and throat disease, cervical arthritis, and other specific physical causes of the headache. Thus one is left with the vast majority of patients having chronic headache. A painstaking examination serves two purposes. First, it assures the physician of what the situation is, so he may be confident in his approach to the patient. Furthermore, practically all patients having headache over a long period of time have considerable anxiety over the possibility of brain tumor, "stroke," blood clots, insanity, or other dreaded diseases. A complete evaluation goes a long way in removing these fears. The extreme concern as to the nature of the headache makes the patient more anxious and nervous, and puts him under considerable tension. After a complete evaluation and a satisfactory explanation of the findings the patients may be definitely improved without the need for more elaborate treatment. The resultant decrease in worry, anxiety, and tension that accompanies the actual attack of headache, or even the anticipation of a headache, frequently removes the main symptom. In taking the clinical history the patient may volunteer many facts that will be of benefit in the later handling of the case. The patient's request for a roentgen-ray examination of the skull, or other studies he may think important should never be belittled, since this request is often the clue to an underlying deep-seated fear of brain tumor or other organic diseases.

FIG. 2



Roentgenogram of skull showing normal calibre of blood vessels.

FIG. 3

Roentgenogram of skull showing increased calibre of blood vessels.

Once we have accomplished this study and have reassured the patient, we use pictures in a textbook or x-ray films of the skull, which we keep in our office for demonstration to the patient, to explain just what happens physically during his attack of headache (Figs. 2 and 3). The patients readily understand, as they look at the picture, that the blood vessels are capable of stretching. They often volunteer, "Yes, doctor, that is exactly how I feel; I feel like the blood just is rushing into the

head and that the head is too small. I feel as if its going to burst, and that picture explains it to me." Now with our understanding of the role of blood vessels, nerves, muscles, fluid retention, and the like, in the production of headache, we should be better able to understand the physiologic patterns through which the patient expresses his individual headache. It is the way that the individual doctor has looked at these physical manifestations that has led so many people in the field to come up with different approaches to therapy.

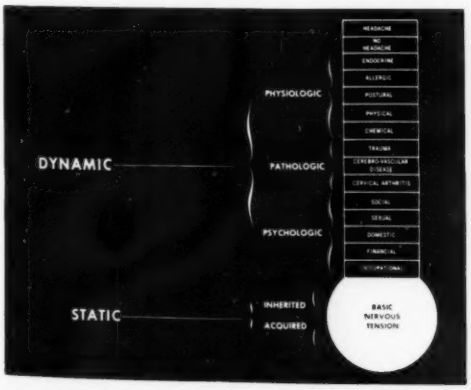
Once we understand what is happening in our patient, the next step is a further thorough discussion with the patient to determine what brings about the pattern of his headache. We keep repeating and re-emphasizing the headache pattern so that we will not "lose sight of the woods for the trees." Most of these patients have repeated attacks and each attack is quite similar to the one preceding. Our job now becomes twofold,—the most difficult part, the most time consuming and most important is to sit down with the patient on one or several, or on as many visits as necessary, and work out the patient's mode of living and determine his background, to get him to understand how he is living and what he is doing to himself.

The simplest way of handling this situation in my office is as follows: We explain to the patient that each of us has a limit to which he can strain his system (Fig. 4).

We explain to the patient that through heredity or through repeated experience, or both, his tissues in and about the head have developed the habit of reproducing the above described symptoms at periodic intervals, and that the thing that precipitates the onset of this pattern can be any stress, strain, change, or modification that occurs in his system. Here it is often of benefit to actually present this graphically. We explain to the patient that he should imagine his headache pattern is all set up and ready to be "triggered off" at any time and that, having had repeated attacks of this pattern, the "trigger" becomes more and more easily discharged. Thus after many such attacks a state of fatigue or tension, which the patient formerly would barely notice, might be enough to precipitate an attack. This whole picture is explained to the patient, and after the complete examination and explanation of actual physical changes during a headache, the patients realize that we are on the right track and wish to cooperate. Before going into these explanations we make sure the patient is actually amenable to that which we are trying to do. We explain to him that from now on most of the work in helping the headache will be on his shoulders and that most of the treatment will depend on his sincere and honest desire to want to get well. We explain that certain ways of lying, certain ways he expended energy and built up anxiety and tension in the past, will have to be recognized and modified. If he does not understand this and does not wish to cooperate completely to get well,—if he really does not want to get well, it is futile to do any more about his headaches. There is no pink pill or panacia that will do the work.

By thus putting the patient "on the spot" and pointing up the problem in this manner, we can tell whether he understands what we are doing and whether he is going to cooperate. If we feel she is only in the office because the husband insisted on it, or is looking for a quick cure we will tell the patient to go home and think it over. When the patient thoroughly understands what we are trying to do and wishes to go into the problem as deeply as necessary then only will we expend the time and energy necessary to help him. Thus we have a receptive patient for the following. We then explain the trigger mechanism and how each one has a limit to which he can strain his system. The more intelligent or should we say the more fortunate individual

FIG. 4



Examples of the various stress-producing factors which added together may produce the attack of headache.

learns early in life the limits he can stand. He learns from example or experience that when he exceeds these limits something unfortunate or uncomfortable happens. This usually shows up physically as fatigue, general nervousness, irritability, tension or as specific symptoms, such as headache, hypertension, gastrointestinal spasm, or any one of a number of other psychosomatic symptoms. He is very wise who recognizes early in life what these symptoms are, or who recognizes what plain fatigue from excessive strain is. We tell our patients that this is the language Nature uses to tell us when we are exceeding our limits. The unfortunate thing is that the average person does not pay attention to those early warnings and persists in straining his system until a more forceful warning or symptom develops. If he is wise he evaluates what this means, or at least seeks medical help for an explanation. Patients who still do not heed these warnings and persist in their bad habits of exceeding the limits of their system will develop still more forceful symptoms and warnings. At such an advanced stage it is more difficult for the patient and indeed for the physician to understand the cause and effect of these symptoms. If the patient has exceeded his limits for a long period of time he will have repeated attacks and will become an expert at developing the particular symptoms. Habit reflexes are set up so the symptoms are reproduced with more facility and much more readily than in the years before. We use the analogy with the patient that his recurrent headache is like a pistol in the top of the head in which the trigger is cocked to go off at any time. When the gun is new and stiff and has not been used much it takes considerable force to pull the trigger and set off the charge, however, after repeated explosions (headache) this trigger becomes well oiled and works much more readily and easily, so that just a light touch suffices to explode it. We then explain to the patient that his body is capable of just so much nervous, physical and emotional strain and tension each day, and if he reaches and exceeds this particular limit it will suffice to pull the trigger and set off the headache.

At certain times of the day or at certain times of the month bodily processes, such as the body getting ready for menstruation, create their own strain and tension on the system so that at that particular time it takes much less externally developed tension and strain to reach the point where the trigger will go off. The wise patient readily understands this. She finds that if, at the time of the month when the headache might be imminent, she avoids strain, she often can get by with much less headache than if she does not pay attention to the way she expends her energy.

Now where does all this discussion in relation to tension lead? It makes no difference whether the body is strained by physical exertion, or by changes in fluid balance as the monthly cycle evolves, or by illness, fever, or any other factor that strains the system. They all serve to use up energy and create tension. In addition, everyday life places us in situations that produce anxiety. These elements of tension that develop from outside, in pursuit of our studies, our jobs, our family and social life, add to the above described physiologic strains of our system. The wise person learns how external circumstances and people affect him. He prevents these external strains from encroaching upon his system and adding to the tensions built up by his own bodily functions. He thus is able to prevent expenditure of energy and "build-up" of tension above that with which his body can cope. With this understanding he can now better control and direct his own affairs, so the emotions and neuroses of others will not influence him and create tension.

As stated before the patient himself is the only one who can apply effective therapy in recurrent headache. The role of the physician is to let the patient talk, to direct the talks to significant revelations, and to suggest the value of a more hygienic mode of life. The average practitioner may wish to throw up his hands and say, "You're trying to tell us we should be psychiatrists." No, most of these patients can be treated in the practitioners office; it takes time, possibly several sessions of one-half to one hour each, certainly worthy investment to put the patient on the road to recovery. All of us have had patients on whom we had to make house calls at all hours of the day and night because of these headaches, and have even needed to take them to the hospital to replace fluids. The prevention of such attacks is certainly worth the expenditure of several hours of time, and actually the general practitioner is in a much better position to

TABLE 2

TYPES OF CHRONIC HEADACHE IN OUR SERIES OF 1,254 HEADACHE PATIENTS

	Number of Patients	*Per Cent of Series*
I. Vascular Headache		
1. Histamine	61	4.8
2. Migraine	465	37.0
3. Hypertensive	16	1.2
4. Temporal arteritis	1	
II. Tension Headache	540	43.6
III. Nonvascular Headache		
1. Muscle tension	12	1.0
2. Major psychiatric abnormalities		
Conversion reaction	5	.4
Psychosis	32	2.4
3. Secondary to diseases of eyes, sinuses or teeth	72	5.7
4. Occipital and facial neuralgias	18	1.4
5. Space-occupying lesions		
Primary brain tumor	2	.15
Metastatic brain tumor	2	.15
Syringobulbia	1	.05
Aneurysm of the major branches of the internal carotid artery	2	.15
6. Post-traumatic	25	2.0
	1,254	100.0

handle these patients than is the psychiatrist. These patients are healthy people, most of them are not psychotic, most of them have just gotten into bad habits, and who is better able to understand this and advise them than their own family physician. What they need is positive psychotherapy, they need positive direction and suggestions as to where they are expending energy foolishly.

Exceptions prove the rule. There are occasional patients who have constant "nagging" headaches. Upon careful analysis it will be seen that these symptoms are actually part and parcel of a "nervous breakdown" usually of a form of a depression. These should be recognized and be referred to a psychiatrist for treatment.

Now we shall try to present a simple classification of headache based on clinical patterns and pathophysiology. This will be illustrated in table 2 of an analysis of 1,254 consecutive patients treated for headache. It appears that most of the cases were diagnosed as vascular tension headache.

Time will not permit detailed discussion of specific therapy for each type of headache. Directions for proper administration of histamine for the histaminic cephalalgia, migraine, and other vascular types are readily available in previous reports. The psychotherapy described above for tension headache can be materially aided by sedation and analgesic compounds such as Fiorinal. The newer tranquilizing agents such as Equanil are also of benefit. Specific treatment of acute vascular headaches, such as migraine, is still based on ergot combinations and derivatives as shown in table 3.

In *conclusion* we would like to re-emphasize several points. (1) Headache in an individual patient is a pattern brought about by mounting stresses and strains of an emotional, physical, or nervous type, or a combination of these, which strains his system beyond its limits. (2) A thorough, detailed history, physical, and laboratory examination, followed by an adequate explanation of the findings to the patient will form the basis of a good understanding of the headache problem and lay the foundation for the rapport necessary to carry out positive psychotherapy. Once this is under-

TABLE 3

ERGOT THERAPY FOR VASCULAR HEADACHES AND THE VASCULAR COMPONENT OF TENSION HEADACHE

Suggested Order of Effectiveness

Medication	*Method of Administration*	*Initial Dose*	*Subsequent Dose*
(Administered by Physician)			
DHE-45	Intravenous	1 cc. = mg.	Not Needed
Gynergen	Intramuscular	½ cc. = .25 mg.	Not Needed
DHE-45	Subcutaneous	1 cc.	1 cc. in one hour?
(Administered by Patient)			
Cafergot PB Suppositories	Rectal	1 Suppository	1 suppository in one hour seldom needed.
Cafergot Suppositories	Rectal	1 Suppository	1 suppository in one hour as needed.
Cafergot PB Tablets	Oral	2 Tablets	1 every half hour until relief or total of six.
Cafergot Tablets	Oral	2 Tablets	1 every half hour until relief or total of six.

stood the patient is instructed in the use of a specific medication to reduce tension; drugs may be used orally, rectally or by injection during the attack. The crux of the whole matter is for the patient to learn the limits of his system and to learn to live within them.

Discussion (Abstract)

Dr. James W. Watts, Washington, D. C. This paper is an important contribution in the management of headache. Most papers on the subject deal with the results of treatment with specific drugs and give comparative results between one medication with another.

All of us have recognized that we are often unable to duplicate the results of an author who describes a new medication. We find, for example, that we cannot get as good results with ergotamine tartrate, an antihistamine, a sedative or an analgesic as the individual who made the report. The paper we have just heard offers an explanation for this, since they emphasize the treatment of the individual. They emphasize the importance of having the patient learn his limits and to live within them. There is no substitute for a careful history. While nervous tension is the precipitating factor in most cases of migraine, an allergic reaction to chocolate precipitates a migraine attack in others. However, the mechanism of the pain is the same,—stretching the nerve pathways in the cranial vessel.

I have enjoyed this paper very much.

What Physicians Should Know About Respirators*

HERBERT KENT, M.D.,† *Oklahoma City, Okla.*

The author gives detailed descriptions of respirators and evaluates the advantages and shortcomings of the various types.

FREQUENTLY physicians have to select equipment for their patients when respiratory impairment is present. In addition, they need to become familiar with the operation and maintenance of the different apparatus presently available today. The care of the patient with acute and chronic disease requires knowledge which is ever changing with continuing modifications by manufacturers.

Since such information is necessary for the management of the patient in a respirator, certain points in general information, as well as some detail will be presented together with opinions based on personal experiences with each type of apparatus mentioned. The ideas presented are not criticisms of a particular respirator, but should serve as a guide for instruction as well as therapy. An understanding of the common features and differences found with each respirator is essential if one is to assist calmly and efficiently when an emergency arises.

Basic Mechanical Features of Respirators

All types of respirators have the common factor of a change in pressure applied to the chest. The methods of reducing the atmospheric pressure around the patient's chest are, (1) the tank-type respirator, and (2) the cuirass, chest-abdomen, or portable respirator.

The following principles are common to these two methods: Rhythmic alteration of the pressure in the respirator substitutes for the normal person's respiratory muscles. The difference between the atmospheric pressure surrounding the patient's head and the lower pressure "in the iron lung" surrounding his chest is responsible for air entering the patient's lungs. In the tank-type respirator bellows alternately produce negative and normal intra-tank pressures. The automatic cycle continues as long as the power unit operates.

In the portable "Monaghan" type of respirator, in comparison with the tank, the design is to supply alternating pressure to the patient's body without enclosing it in larger tanks. A small portable power unit and bellows delivers alternating pressures to the patient's chest directly through a connecting tube. The chest piece encloses only the anterior and lateral chest allowing the patient more comfort while in bed. Other portable types of respirators are on the market; the cuirass may either enclose the chest only, the chest and abdomen, or completely enclose the upper half of the patient's body.

Tank Respirators

Port Holes and Head Collars. The port holes in the tank respirator permit the attendant, therapist or nurse to care for the patient inside the respirator, and are so placed, one or more on either side of the chest, to facilitate positioning, bathing, and the checking of the pulse and blood pressure. The bedpan port, usually larger and of rectangular shape, is for placing the pan inside the respirator without losing an appreciable amount of pressure. Urinals, wash basins, small pillows and the like may be placed inside the respirator through this opening. Ports in the middle and end of the respirator are for positioning and for such procedures as taking rectal temperatures, giving enemas, for catheterizations, and changing or draining of a Foley catheter. Port gaskets are made of sponge rubber or a plastic material to be used in a "spiratwist" type frame. They must be changed frequently or as necessary, often as much as daily. They may be changed in as

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little time as five seconds; the speed with which an attendant changes these gaskets is most important. The head collar is the entrance for the patient's head and neck. The material may be either of sponge rubber or of plastic on a "spiratwist" plate (Fig. 1). The "spiratwist" collar is the better collar allowing a more secure seal with less sweating and irritation of the neck. The head is supported by a hammock-type frame or a stationary head support usually adjustable by a hand wheel. The collar is adjustable and the patient may be turned to either side or back with an adequate seal of the collar. These collars are changeable, and must be changed rapidly should a tear or hole appear.

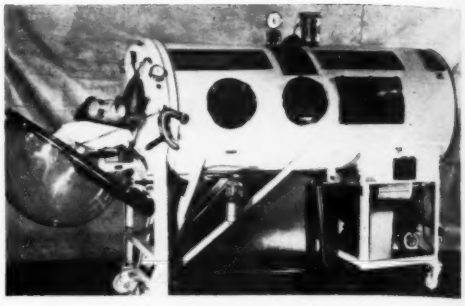
Pressure Gauge. The gauge permits attendants to check the pressure received by the patient. It must be observed frequently for changes which might suggest openings or an insecure seal. The gauge is watched at any time the respirator is to be entered. The average pressures for the tank are 15 to 20 cm. of water; for the portable, 10 to 15 mm. of mercury.

Respiratory Rate. The rate wheel of most respirators is so constructed that it may be operated at several speeds, usually varying from 14 to 36 respiratory excursions per minute. The respiratory rate is set *before* the patient is placed in the respirator and may need to be readjusted to the patient's special needs. The operation of the rate wheel, usually found near the motor, is simple. A twist to the right increases the speed, to the left, decreases the rate.

FIG. 1

"Spiratwist" collar with depressor for tracheotomy.

FIG. 2



Tank respirator to show features.

Hand Operation. In case of failure of the electric current or upon transportation of the respirator, it is necessary to operate it by hand. The different types of respirators, both the tank and other types, have hand levers which are easily applied, and operation of the respirator by hand can be started in less than one minute. Hospital personnel, both professional and nonprofessional, should know how to change the respirator from electric to hand operation.

Mattress and Bed Trough. The mattress should be of foam rubber completely enclosed by a sealed rubber sheet so that should the bed linen become wet or soiled, a change of linen only is required. The entire bed can be pulled out of the respirator, allowing the attendant to care for the patient.

Type of Respirators.

Emerson Respirator. (Fig. 2) If the design features of the Emerson Respirator are understood they will assist in learning the location of essential and principal features of all. It has a *concave* head plate and locks to the tank body by two hand locks. There are 5 large arm ports, two inches larger than in other tanks, and one large rectangular bedpan port. There is a control panel with an "on-and-off" switch. The pressure gauge is of the rotating type. As with all respirators, there is a lever for hand operation. The bellows is of the diaphragm type. A hydraulic jack is present for raising the tank into the Trendelenberg position. There are

accessory outlets. Unlike other types of respirators, there are arm sling supports. The bed trough is adjustable and the bed may be turned to either side, raised or lowered. The head support is of the stationary type but is adjustable. The mattress is of sponge rubber and enclosed in a sealed rubber sheet. The neck collar is of the "spiratwist" type. Sponge rubber gaskets are found on all the arm ports. The operating technic requires the knowledge of several basic features.

The Emerson is operated by means of a leather diaphragm at the end of the respirator. The diaphragm becomes convex or "pushed outward." An inhalation registers as negative pressure on the gauge. The respiration *rate* wheel is placed to the left of the A.C. motor unit immediately below and forward of the D.C. motor or to the right when only a single motor is present. The rate wheel rotates to the *right to increase* respiration and to the *left to decrease* the rate. The respiration depth wheel is placed in the center of the respirator below the main tank body. Turning the hand wheel to the right increases and to the left decreases the depth. (The pressure gauge must be closely observed in this maneuver.) The pressure gauge is found on the top and center of the respirator, and may be completely rotated to permit the attendant to observe the gauge from any location. Hand operation may be started by pushing down the lever at the base of the diaphragm at the rear of the respirator; this lever is on the lower end of the rocking beam. To change back to the electric current, the lever is returned to its original position until the catch engages.

Accessory openings on the head plate and in the center at the top of the respirator, immediately behind the pressure gauge, may be used for the introduction of intravenous tubings and the like. A support for the intravenous bottle is provided and may be attached to the head plate or in a socket. This respirator apparently is the only one with such a device. Swinging rods on the inside of the head plate are for the support of the paralyzed arms in slings. Two spare outlets are provided for electrical devices.

The advantages of the Emerson Respirator are:

1. Hand operation is easy because of accessibility of hand lever.
2. There is a rotating pressure gauge.
3. The motor switch for operating the respirator is present.
4. The concave head plate allows more working room around the head and throat.
5. There is an adjustable head support.
6. Arm supports are found inside the respirator.
7. Larger and comfortable arm ports.
8. A larger bedpan port.
9. An A.C. and D.C. motor, when two are supplied.
10. Two electrical outlets on the tank body.
11. Large rubber covered mattress and bed trough.
12. Accessory outlets.
13. Intravenous support.

The disadvantages of the Emerson Respirator are:

1. It is larger, therefore, it is more difficult to move around the room.
2. It is heavier and takes more personnel to lift the respirator should the occasion arise.

Drinker-Collins Respirator.

This respirator has similar design features to the Emerson but the following differences are important to note:

1. Convex or sloping head plate.
2. Arm supports.
3. Sponge rubber gaskets which, however, may be changed to a "spiratwist" frame.
4. Bedpan port.
5. *Stationary* control panel and pressure gauge dial.
6. Accordion-type bellows.
7. Emergency hand operation.
8. Three head locks.
9. A.C. motor unit.
10. Accessory outlet.
11. Motor and light switch.
12. Rubber-covered foam rubber mattress.
13. Hydraulic jack for Trendelenberg position.
14. Viewing windows.
15. Hammock-type head support.

The Drinker-Collins operates by means of accordion-type bellows, attached to the under surface of the tank, which expands for negative pressure and contracts or folds up for expiration. The control panel is located on the right side of the respirator. The pressure control knobs, motor and light switches are located on either side of the pressure gauge. The knobs "for pressure control" are rotated to the right for increase, to the left for decrease. The rate of respiration is adjusted by using the hand wheel immediately to the front of the motor unit. The handle for manual operation is usually located underneath the *right side* of the respirator and is fastened with a *thumb nut* which may be unscrewed. The respirator bellows is operated by means of two lever bars which are connected by a box-shaped c-clamp. Loosen the clamp and pull it forward to the stop pin on the longer of the two levers, and then connect the handle for manual operation by tightening the box clamp.

The advantages of the Drinker-Collins Respirator are:

1. The hammock type head rest may be removed completely allowing more room for procedures such as tracheotomy or bronchoscopy.
2. The Drinker-Collins is not as heavy as the Emerson nor as large, allowing easy movement of the apparatus, and less floor space is necessary.
3. More ports are located on the Drinker-Collins.

The disadvantages of the Drinker-Collins Respirator are:

1. The ports are not as large as those in the Emerson Respirator causing limited range in movements of the attendant's arms.
2. Head support is not freely adjustable.
3. The tank cannot be closed as quickly with a three hand lock at the head plate.
4. Hand operation handle takes longer to be adjusted than does the Emerson.
5. Respiration rate wheel is not as accessible as the Emerson's.
6. It does not have a D.C. motor.

7. It has only one accessory outlet and no electric outlets.
8. The rotating bed is harder to adjust requiring assistance from a second attendant.
9. It has no arm support.
10. The convex head plate when present takes up too much room in the vicinity of the patient's throat.

Fabrikator Respirator.

The Fabrikator Respirator utilizes several of the features of the Emerson and Drinker-Collins. It has the following design features:

1. Convex head plate.
2. Viewing windows.
3. Eight ports with "spiratwist" or sponge rubber type frames.
4. Rotating bed.
5. "Spiratwist" collar frame.
6. Accessory outlet.
7. Stationary pressure gauge.
8. Rubber-covered foam rubber mattress.
9. Adjustable head support.
10. Emergency hand operation.

The operating technics are somewhat similar to Drinker-Collins. It operates the same type bellows; hand operation is the same, however, the *handle is found under the right front leg of the tank support.*

1. Negative pressure is secured by closing the front flap with the hand screw at the head of the tank.
2. Machine is in operation when the electric cord is plugged into the wall outlet. (Newer types have an "on" and "off" switch.)

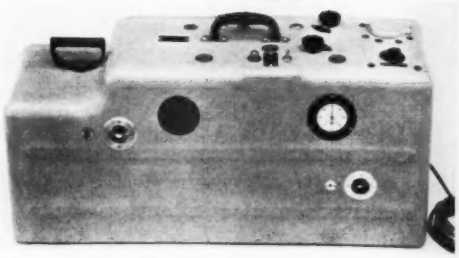
The advantages of the Fabrikator Respirator are that:

1. It is smaller and more compact than either of the other respirators.
2. There are more arm supports than the Emerson.
3. It can be a duplex machine allowing two children to be placed in the same respirator (also may be found with Drinker-Collins).

The disadvantages of the Fabrikator Respirator are:

1. The ports are too small and limit the range of motion.
2. Pressure gauge is not of the rotating type.
3. Head support is insecure and does not support a large enough pillow.
4. Port gaskets when made with "spiratwist" type frames, one must use the "spiratwist cuffs." These cuffs do not seal properly.
5. Manual operation cannot be initiated as quickly as is needed.
6. Viewing windows are small and rather high on the respirator.
7. It has no arm support.
8. The respiration rate wheel is very unhandy and vibration of the machine sometimes causes the wheel to slip, thereby changing the rate of respiration.
9. The bedpan port is not as large as the Emerson or Drinker-Collins.
10. It has only one accessory outlet.
11. Bed is not wide enough.
12. Mattress does not easily fit into the bed trough.

FIG. 3



Portable "non-tank" type (Monaghan) respirator without batteries, hose, or shells. Note left hand lever for manual operation.

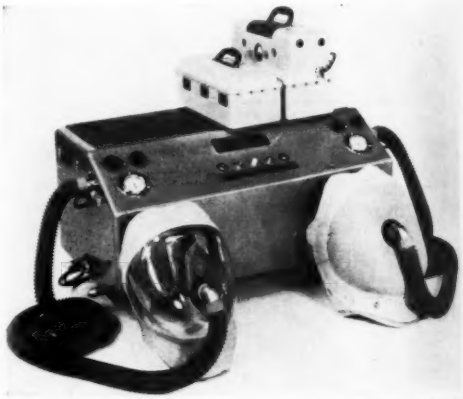
13. One is unable to attach positive pressure machines like the "Bennett Positive Pressure."
14. There are no electrical outlets on the tank.
15. There is no control panel (newer types have "on" and "off" as well as light switches).
16. There is no attachment for bottle for intravenous indications.

Non-Tank Type Respirators

These respirators have become exceedingly popular because of their portability and comfort to the patient. Three popular types are on the market in this country. They are the Monaghan, Technicon-Huxley and Emerson, and are quite different from one another and very frequently are so modified that it is not practical to name the mechanical features of each at this time. However, the design features should be understood and compared with the large tank-type respirators.

These respirators are designed for portability or mobility. The units come in several

FIG. 4



Monaghan Hospital Respirator with battery, rectifier, and shells for dual operation.

sizes and with several chest frames. The frames are usually made of plastic material for lightness; a flexible hose connects the motor unit to the chest frame. Canvas, plastic or other type straps are used to adjust the chest frames to the patient's chest. Each portable motor unit has its own auxiliary emergency battery supply, and each has a hand operation lever (Fig. 3). All have a central control panel with pressure gauge and control knobs for negative and positive pressures. There are also levers or knobs for adjusting the respiratory rate. Some of the models may be used for two patients at the same time.

The operating technics are more or less uniform. The proper sized chest piece must be at hand for the individual patient. The motor unit may be adjusted to use either a battery or the alternating current. The respiratory rate may be adjusted. The switch for the motor unit is usually found on the control panel. One must adjust the "negative" pressure knob to obtain anticipated negative pressures. The canvas, plastic or other type of straps are to be placed under the patient's back before adjustment of the chest frame is attempted. The chest frame is applied with the curves of the frame corresponding to the patient's chest by fastening the straps and fitting the frames snugly to the patient's body. Some units are applied directly to the patient's skin and others use intervening cotton material to prevent chaffing.

In operation, the flexible hose is attached to the motor unit, and then fastened to the chest frame by fitting the large metal or plastic connector into the socket of the chest frame. Hand operation may be accomplished by removing the back of the unit or by a small hand lever at the side. The location of the hand lever varies a lot in portable respirators.

The limitations of such apparatus are that they can be used for short periods, and may become uncomfortable to patients with any kind of abdominal distress. In addition, the patient is unable to turn on his side. Its advantages, however, outweigh its limitations:

1. It is portable and may be used for transportation purposes.
2. May be used in emergencies where the tank-type respirator is unavailable or cannot be transported.
3. The patient may sit in a wheel chair with the non-tank respirator in operation.
4. It is small and compact and takes up very little room in hospital or ambulance.

Operation of Portable Respirators. There are three commonly used portable respirators available at the present time. Monaghan (Universal Model), Technicon-Huxley (Chest-Abdomen), Emerson (H.B. or C.R.I. Model). An older Drinker-Collins Model may also be found in some hospitals resembling the Emerson H.B. Model. The respective total weights of these portable respirators are 125, 185, and 200 lbs. The weights of the batteries are usually included in the total weights.

The portable respirator may be operated on three sources of power usually: regular house or hospital current—110 volts A.C.; battery current of 24 volts D.C.; manually. The Emerson H.B. Model and Drinker-Collins portable model do not operate on battery current. The older model of the Monaghan Respirator has to operate on 12 volts D.C. current.

Application of Chest Piece

1. *Preparation of skin:* The skin should be checked for signs of irritation and, if possible, pressure should be eliminated from those areas. Cleanse and powder the skin area where respirator shell will fit. A tight fitting thin cotton T-shirt or similar material between the patient and the respirator shell is advisable. This is particularly important if the patient is to be in the respirator for a long period of time. Stockinette is also good material. Loose clothing causes leaks.
2. *Preparation of shell:*
   a. Use the largest shell that will fit the patient. The larger the shell the more comfort and the greater chest expansion possible. Too small a shell gives inadequate ventilation and causes great discomfort. Loss of weight or a chest deformity makes a seal extremely difficult.
   b. Attach the shell to the operating unit and have the power on *before* the shell is fitted to the patient.
   c. Deflate the rubber area or seal slightly if one is present. Do not over inflate.
   d. Put the straps under the patient, apply the shell and adjust the straps accordingly.
   e. If necessary the shell may be held tightly in place by hand while other preparations are made.
   f. Control small leaks using sponge rubber if necessary.

Selection of Pressures

1. The rate and depth of respiration will be controlled by the nurse or physician according to the individual patient's needs.
2. Before the shell is applied, the negative and positive pressure knobs are set. Settings are only temporary and should be adjusted to the patient's needs after artificial respiration has been established.
3. It is important to note that pressure may be in millimeters of mercury or centimeters of water pressure.

The Monaghan Portable has a gauge calibrated in millimeters of mercury pressure. Average pressures with a Monaghan are 15 to 20 mm. of mercury for adults and 10 to 15 mm. of mercury for children. With

portable models, such as the Technicon-Huxley and Emerson where the pressure gauge is in centimeter of water, average pressures are 20 to 30 cm. for adults and 15 to 20 cm. of water for children. If there is a drop in the pressure or the pressure cannot be obtained, check for an air leak around the shell or the hose connection before adjusting the pressure knobs. Respiratory rates are usually 14 to 16 per minute for adults. Gradually increased rates are used for infants and children. If the patient has any voluntary respiration, set the respiration rate with their own rate regardless of how fast it is. After the patient has become accustomed to the respiration and is synchronizing with it during all phases of respiration, the rate can be changed.

Points to Remember:

a. When storing the shell, its open edge should be placed downward and its dome uppermost, to prevent breakage and distortion.

b. The hose should be inserted into the metal fitting of the shell gently, with a twisting motion, since force will ruin the connection.

c. When applying the shell to the patient, grasp the open edge on either side and spread them slightly apart to accommodate the rib cage.

d. Adjust the straps to a comfortable snugness sufficient to maintain a leak proof connection. Do not adjust the straps too tightly.

e. Inflate the seal slightly whenever indicated to overcome leakage. An over-inflated seal will also cause leaks.

f. Heat will distort the shape of the plastic and cause rubber to deteriorate so the shells should not be stored near a radiator or in the sun.

g. If there is a battery unit, it should be kept at a fully charged state at all times.

Battery Operation.

A fully charged battery will last approximately 6 hours or longer before recharging. For an emergency two fully charged automobile twelve-volt batteries connected in series will operate the power unit for approximately 15 to 20 hours.

A. *Monaghan Portable.* (Fig 4) The battery unit is usually attached to the respirator, and in case of power failure, the unit will automatically switch to the battery. When the house current is again available, the respirator will automatically switch back to house current operation. When the respirator is connected to both a wall outlet and a battery, it will automatically derive its power from the house current only. The Monaghan has a built in recharger and the battery can be recharged either while it is connected to or disconnected from the power unit. Full directions accompany the apparatus relative to charging the battery.

B. *Technicon-Huxley.* In the case of the Technicon-Huxley Respirator the power unit comes in two parts, battery and Rectifier-Charger. (There are both a Technicon-Huxley portable model and hospital model.) The portable is designed to run directly on 24 volts D.C. or 110 volts A.C. of the Rectifier-Charger.

Information in respect to battery operation and charging is essential with the Technicon-Huxley portable model and accompany the instrument.

C. *Emerson.* The Emerson Chest Respirator is more mobile rather than portable for it weighs approximately 200 pounds. The Drinker-Collins type is similar but weighs only approximately 100 pounds. Both of these operate from standard lighting circuits, 110 volts A.C. or by hand. The Emerson Chest Respirator consists of 8 chest shells, 8 hose adapters, and 4 sheet plastic wraps, all of which makes this type of a portable respirator rather unwieldy and confusing. However, the operation is satisfactory once it has been adjusted to the patient.

Manual Operation. All portable units may be operated by manual pumping or emergency hand operation.

A. *Monaghan.* Provision is made in the Monaghan Respirator for manual operation in the event of either nonavailability of proper electrical source of power or mechanical failure of respirator, respiration can still be maintained. Directions are provided with the instrument.

B. *Technicon-Huxley.* A handle is used for manual operation. The crank can be found in the cabinet and is easily assembled.

C. *Emerson.* Hand operation is instantly available without any adjustment or disconnections of any sort since the handle actuates a piston which is independent of the motor driven piston.

D. *Drinker-Collins Portable.* The handle for the Drinker-Collins apparatus, found in the cabinet, is attached to the box clamp adjoining the bellows in the same fashion as on the tank type respirator.

Check List for Respirators

A. Check the amount of pressure prescribed.

B. Check the rate of respiration.

C. Know that all the seals are securely closed.

D. The machine should be running smoothly. Watch the gauges.

E. The electric cord should be securely attached in a wall socket or battery operation should be firmly established.

F. There should be no air leakage.

G. Locate the manual operating lever and know that it is ready for emergency use.

Summary

Comparison of "tank" and "portable" respirators are described. For each of the more common types, the design feature, operation points, as well as advantages and disadvantages are given in some detail.

Discussion (Abstract)

Dr. Rachel F. Weems, Ashland, Va. Dr. Kent is to be congratulated on his excellent paper. This is a subject about which little can be found in the literature; I realized this when I checked the library of a near-by medical college. Many of us have learned about the different respirators through the experiences and demands of a poliomyelitis season, but it is nerve-wracking and frustrating when time is precious.

The physician who has to select a respirator will find the list of advantages and disadvantages of help in selecting the type to meet the special needs of his patient. The discussion of the design features and operation gives him a better concept of the machine he has selected.

The author draws upon his broad experience to offer suggestions and necessary precautions in the operation of the various types of respirators. I was glad to see that he went into detailed description of how each was operated manually. This is a most important item. It is also desirable that the person responsible for that particular respirator shall have practiced its manual operation. Current does go off every now and then, but if the nurse knows what to do the change-over is done without undue panic or excitement.

The full discussion of the non-tank or portable respirators is extremely helpful, because of the popularity of this type. Some physicians may have occasion to use these more frequently than the tank type and will appreciate the help given here.

I thank Dr. Kent for the opportunity of discussing his paper and again congratulate him on presenting so much information so concisely.

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Management of Acute Nephritis*

WILLIAM J. A. DeMARIA, M.D.,† *Durham, N. C.*

The author considers the vascular element in acute nephritis and the treatment directed toward this.

A BRIEF SUMMARY and interpretation of knowledge concerning the etiology and pathophysiology of acute glomerulonephritis will be presented in the hope that this discussion will serve as a rational basis for the management of the child with acute nephritis.

Etiology

An infection with any one of the more than forty types of beta hemolytic streptococci in Group A usually prompts an immunity to one or more of the antigens found in that specific streptococcus. In the average community with a streptococcal epidemic those individuals with the least previous streptococcal experience, usually the children, will have the highest incidence of the disease. Complications of streptococcal infection should be most frequently seen during the age period of highest incidence.

Since two-thirds of the cases of acute nephritis occur in children under the age of seven years and the majority of these give a history of preceding streptococcal infection, a cause and effect relationship has long been suspected. However, many patients with acute nephritis give no history of streptococcal infection nor do they harbor streptococci on routine survey. Another puzzling feature is that in some epidemics caused by beta hemolytic streptococci few or no cases of acute nephritis will be noted, whereas in other epidemics the rate of acute nephritis will be alarmingly high.

The problem has been considerably clarified by the finding that only specific types of beta hemolytic streptococci in Group A are associated with a high incidence of acute nephritis.[1] Thus far type 12 is the most common streptococcus associated with acute nephritis, although other types have also been implicated as nephritogenic streptococci.[2,3]

Although the specific mechanism through which these streptococci provoke this nonsuppurative complication has not been entirely defined, current evidence is sufficient to warrant the physician's consideration of prophylactic measures in potentially susceptible people when such type specific streptococci invade the community.

Clinical Variants

Once the process of acute glomerular nephritis is initiated a wide spectrum of response occurs in different patients.

The condition may be so mild as to escape detection by history and physical examination, but a urinalysis will reveal changes characteristic for the disease. At the other end of the clinical spectrum is the patient who has an acute onset of anuria, anasarca, hypertensive encephalopathy, apparent heart failure and death. The majority of patients are those who have an onset of edema, usually periorbital at first, and bloody urine, associated with the findings of an elevated blood pressure and the characteristic urinary findings.

Less characteristic cases may pose diagnostic problems. We have observed an occasional child with an acute onset of generalized convulsions associated with an elevated blood pressure but no discernible edema, and a normal urine for the first one to three days of hospitalization. Other children were admitted to the hospital because of sudden onset of total blindness. An elevated blood pressure, but again without edema, but with a normal urinalysis were found. Other patients may present themselves with generalized edema, an elevated blood pressure and normal urine. Similar cases have been seen by other authors who include autopsy reports to verify the pathologic findings characteristic for the disease despite the "normal" appearing urine.[4-6]

*Read before the Section on Pediatrics, Southern Medical Association, Fiftieth Annual Meeting, Washington, D. C., November 12-15, 1956.

†From the Pediatric Department, Duke University School of Medicine, Durham, N. C.

These cases are emphasized because they serve to focus our attention on the generalized nature of this disease, and indicate that the renal involvement is to be considered as part of the process rather than the sole or major area of disease.

Pathology and Physiology

The majority of those who develop acute glomerulonephritis survive, and most of those who expire do so within a few days after the onset of the clinical course. Studies of people dying within one to three days of onset reveal that almost all of the glomeruli are involved, the earliest change being a dilatation of the capillary loops which are practically devoid of blood, but are filled with a "coagulated protoplasmic exudate."[7] Within a short period the lumens of the capillary loops are blocked by exudative and proliferative processes resulting in practically a complete ischemia of the glomerular tufts. During this early phase hemorrhage may occur into the capsular spaces. Leukocytes, coagulated protein and fibrin may also be seen in these same capsular spaces.

The observation and opinions of Volhard are particularly pertinent at this point.[8] In addition to commenting on the paucity of red blood cells in the glomerular capillaries he noted that the afferent arterioles were similarly devoid of red blood cells. He reasoned that if the proliferative and exudative process were responsible for the glomerular capillary ischemia then the afferent arterioles should contain blood. As these vessels contained little or no blood, and since no organic lesion could be seen in the walls of these arterioles, he felt this situation could be based on an arteriolar spasm of those vessels leading to the afferent arterioles of the glomeruli.

He further postulated that the arteriolar spasm was not limited to the kidneys but was more generalized. Such generalized arteriolar spasm could account for the peripheral hypertension, the occasional retinal lesions, and the edema (by causing ischemic injury to the capillaries secondary to the arteriolar spasm).

In support of Volhard's theory are measurements of the protein content of edema fluid which reveal values close to the plasma level.[9] However, with the sampling technics utilized one cannot rule out contamination from punctured capillaries. Stead's finding[10] of protein levels of less than 0.4 Gm. per 100 cc. would appear to rule out increased capillary permeability as the cause for edema, but as Bradley[11] pointed out the small samples were taken from areas of gross edema. This may cast doubt on whether the sample was truly representative of edema fluid as it is initially formed.

Doubt was also cast on Volhard's theory when reports[12] on the indirect measurement of renal function in patients with acute nephritis revealed a normal renal blood flow but a decreased glomerular filtration rate. However, it has been noted[13] that these measurements were made mostly on adults and not in the very early phase of acute nephritis. Other studies utilizing similar technics for the measurement of renal function, confirmed the finding of a decreased glomerular filtration rate but in addition showed a significant decrease in the effective renal blood flow.[13] Support for Volhard's theory was demonstrated by an immediate and significant increase in the glomerular filtration rate and the effective renal blood flow with administration of a known vasodilator, magnesium sulfate. It was also shown that the encephalopathy could be controlled with magnesium sulfate without appreciable lowering of the blood pressure and that severe retinal arteriole spasm could be observed to disappear with the intravenous administration of magnesium sulphate.[13] These observations support further the concept of generalized arteriolar spasm.

Since the signs and symptoms of encephalopathy can be controlled in about ten minutes with intravenous magnesium sulfate, serious doubt is cast on the opinions of those who believe this syndrome to be secondary to the increased intracranial pressure caused by cerebral edema. Although cerebral edema may be a factor in the encephalopathy it is probably not the primary cause, since control is manifest in a matter of minutes after a vasodilator drug is injected. Dramatic evidence that cerebral vasospasm exists is seen in those children admitted because of total blindness who are able to see in 15-20 minutes following intravenous administration of magnesium sulphate.[14]

The sequence of events noted in the renal response to intravenous magnesium sulphate also speaks in favor of the existence of arteriolar spasm. A significant increase in both the

glomerular filtration rate and effective renal blood flow occurs within 5 to 10 minutes after starting magnesium sulphate therapy. Associated with this is an increased urinary output. It would be difficult to explain this consistent and immediate effect on renal function by any mechanism other than relief of vasospasm in the renal network. It is interesting to note here that the occasional child who has been anuric for at least twenty-four hours will show the same immediate response as do those who are only moderately oliguric.[14] Near normal or normal values of the effective renal blood flow returned in about one to two weeks following subsidence of the acute signs and symptoms of acute nephritis.[13] Incidentally, normal controls do not show any significant changes in renal dynamics or blood pressure during this type of treatment.[13]

It has been of particular interest to note in occasional patients, upon initiating magnesium sulphate therapy, the immediate renal response mentioned above and control of encephalopathy before a significant drop in the elevated blood pressure has occurred. Further, in those cases where insufficient magnesium had been given, either intravenously or intramuscularly, to lower the blood pressure for a prolonged period, the symptoms of hypertensive encephalopathy did not return even though the blood pressure may have returned to the original level.[14] It would appear that this chemical relieves vasospasm in cerebral and renal areas at lower levels of serum magnesium than is required for the more general arteriolar dilatation which is necessary before a drop in blood pressure occurs.

Treatment

The following discussion of the management of acute glomerulonephritis is based on the hypothesis that the disease once established provokes a generalized vascular process with arteriolar spasm as the primary manifestation, and with altered capillary permeability as the end result of the vasospasm. This assumption is based on the various pathologic, physiologic, and clinical findings and observations discussed in the preceding sections of this paper.

With this basic assumption the extreme variations in the clinical pictures, as well as the selective clinical involvement of, for example, the kidney, the central nervous system, the pulmonary and cardiac or the general vascular system are better understood. That the kidneys are the most frequently involved area may in part be explained by the fact that the arteriolar pressure in the renal arterioles is considerably higher than arteriolar pressure elsewhere in the body. This higher pressure may cause a greater "leakage" of protein and cells through the walls of the damaged glomerular capillaries. It would also help to understand why the process of renal recovery requires such a long time as compared with other manifestations of the disease.

Proper therapy should quickly accomplish the following:

1. Control the signs and symptoms of encephalopathy and prevent their recurrence.
2. Increase the effective blood flow to the kidneys and increase the filtration rate.
3. Increase the volume of urine output.
4. Increase the output of sodium and chloride in the urine.
5. Lower the peripheral blood pressure.

To control convulsions immediately may prevent damage to the central nervous system. To enhance renal function so as to relieve the patient of the excess salt and water will either prevent or relieve overloading of the cardiovascular and pulmonary systems, and to lower the blood pressure may also relieve the heart of an additional strain.

Antihypertensive or hypotensive agents which have been or are being used in management of patients with acute nephritis and comments regarding undesirable effects are as follow:

Priscoline (2 benzyl—4, 5 imidozoline).[15] This drug induces a neurogenically mediated afferent arteriolar vasoconstriction even in normal humans resulting in a marked fall in renal blood flow and glomerular filtration rate.[16] Since the renal dynamics in acute nephritis are already depressed it would appear that this drug would be contraindicated.

Hexamethonium. Smith's experience with this drug in controlling hypertension of acute nephritis has not been encouraging.[17]

Veratrum and its derivatives. Royce[18] found alkavervir to be effective in controlling hypertension. However, an initial decrease of renal blood flow and urine output, would not appear to be a beneficial effect even if only transient.

Reserpine (Rauwolfia). This drug requires one to one and a half hours before the antihypertensive effect is significant. Renal studies performed during the period of one and a half to two and a half hours after

injection revealed a further decrease in renal function. Studies during this same period revealed a further decrease in urine and sodium excretion.[19]

Hydralazine (Apresoline). Although quite effective in controlling hypertension it also depresses renal function.[20]

Combination of reserpine and hydralazine. It appears that reserpine potentiates the effect of hydralazine and thus effectively controls the hypertension without the necessity of using large doses of hydralazine. However, no consistent beneficial effect upon renal function occurs and in addition there is an immediate and temporary decrease in urinary output.[19,21]

Magnesium sulfate. Administered as described below this drug: (1) quickly controls encephalopathy (5 to 15 minutes), without further recurrences; (2) increases the effective blood flow an average of 42 per cent (range 7 to 76 per cent) and the glomerular filtration rate 24 per cent (range 3 to 55 per cent) within 5 to 10 minutes; (3) increases urinary output within 5 to 10 minutes; (4) increases the sodium excretion fivefold; and (5) controls the hypertension.[13,14]

It is apparent that of the available drugs or drug combinations magnesium sulphate is the only one which fulfills those prerequisites for drug treatment listed in this discussion.

As with all medications a dosage schedule must be worked out to utilize the advantages of the drug and to avoid any undesirable side effects. It has been demonstrated that the effective level of serum magnesium is about 5.6 mEq/L or 7 Mg% (normal 2-3 mg.% or 1.6-2.5 mEq/L).[13,22,23]

To attain this level quickly and safely 200 to 250 mg. of $MgSO_4 \cdot 7H_2O$/Kg. is administered intravenously in about 60 to 75 minutes. This priming dose is calculated using the weight of the child at the time of treatment. This is made up with distilled water as a 3 per cent solution.* It should be emphasized that this dose has been calculated such that it can be administered in the allotted time period to a child who is anuric. Once the blood pressure has been ascertained, the intravenous solution is started at 3 to 6 cc. per minute. If the child complains of "feeling hot" and is uncomfortable because of this, the rate is slowed to 1 to 2 cc. per minute until this sensation disappears. The infusion can then again be increased to the original rate. If the blood pressure does not change, this rate can be continued until the total dose has been administered. If the blood pressure starts to drop, the rate can be slowed slightly or moderately depending upon the degree of change in blood pressure. Usually about one half of the total dose is given in about twenty minutes, the remainder being given in the next forty minutes. Although a vial of calcium chloride is always kept available, its use as an antidote has never been required in our group.

Following this priming dose, 0.3 to 0.4 cc/Kg. of a 25 per cent solution of magnesium sulphate is given every six hours intramuscularly. This is usually stopped by the third day.

In the past five years we have managed 250 cases of acute nephritis. There have been no deaths in this group. There have been no failures in controlling signs and symptoms of encephalopathy, apparent cardiac failure, or severe oliguria or anuria. In three of these cases the blood pressure did not return to normal with the above therapeutic routine although their edema and encephalopathy, if present, were controlled as in other cases. When serum magnesium levels in these cases were determined they were found to be 5.5 mg. per 100 cc. or less which probably accounts for the failure to adequately control the blood pressure. It should be noted that the blood pressure in these cases returned to normal within 7 to 14 days.

As stated above the effective level of serum magnesium is about 5.6 mEq/L (7 mg. per 100 cc.). The toxic level of magnesium or the level at which severe respiratory depression occurs is about 16.6 mEq/L (20 mg. per 100 cc.). Therefore, there is a wide range of safety in use of this drug when administered as above.

In addition to magnesium sulphate we advise complete bed rest. In view of the evidence presented for renal arteriolar constriction bed rest would appear to be beneficial, since the upright position both in normal persons and in the presence of acute nephritis causes a reflex renal vasoconstriction. As noted earlier we have found that the renal blood flow returns to normal in approximately two weeks after the child is free of edema and normotensive. It would seem logical then to advise bed rest for a minimum of one month and the various modifications of bed rest thereafter until the urine is normal.

Initially a low sodium diet is advised, but it is usually safe to discontinue it after the child is edema-free and normotensive. A full nine day course of penicillin is given to eradicate

*A more than sufficient amount for the average case can be prepared by diluting three 10 cc. vials of Parke Davis 25% $MgSO_4 \cdot 7H_2O$ solution to a total of 250 cc. with distilled water.

any foci of streptococci. Prophylactic penicillin, 200,000 units orally per day, is given until the child is considered cured. In our clinic we do not consider the process completely resolved until two Addis counts one month apart are normal.

Digitalis is indicated, in cases with apparent heart failure, although if prompt diuresis occurs the apparent failure quickly subsides.

Three of our patients with acute nephritis were extremely interesting in that they required from between 18 and 22 months before the urines became normal. Follow-up studies have revealed no evidence of renal or vascular disease. As a result we are quite cautious in considering a child to have subacute or chronic nephritis because of a persistence of a trace of albumin and an abnormal sediment beyond a year.

Conclusions

Further evidence has been presented to emphasize the importance of considering acute glomerulonephritis as a disease which is either associated with, or caused by generalized arteriolar spasm. It is believed that capillary permeability is increased because of the ischemia induced by the vasospasm.

Magnesium sulfate is considered the best single therapeutic agent available for management of the various problems associated with this disease in its early acute phase.

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Treatment of Chromophobe Adenoma of the Hypophysis*

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This is an evaluation of the radiation therapy of chromophobe adenomas with and without the addition of surgical treatment.

CHROMOPHOBE ADENOMAS of the hypophysis are histologically benign neoplasms derived from cells which have no known secretory function. They have clinical importance from effects of their expansion on neighboring structures, effects which are frequently disabling for the patient, and sometimes may threaten life. The direction of expansion by these tumors depends upon the relative strengths of the bony floor and walls of the sella turcica and of the diaphragma sellae. It follows that an adenoma may produce its effects by pressure erosion of the bony sella, by compression of the endocrine and neural components of the hypophysis, or by compression of the optic chiasm and/or its proximate neural pathways, of the hypothalamus or the floor of the third ventricle, and even of inferior portions of the frontal and temporal lobes.

Symptoms

It is convenient, therefore, to consider manifestations of hypophyseal chromophobe adenomas by symptom-groups which reflect the direction of their growth:

1. *Headache.* Expansion against the bony walls and stretching of the diaphragm of the sella may account for headache in the absence of increased intracranial pressure, accompanied by radiographic evidence of enlarged sella.

2. *Visual loss.* Decrease in visual acuity and progressive diminution in visual fields.

3. *Endocrine dysfunctions.* Amenorrhea in the female, sterility and loss of libido, aspermatogenesis in the male, decreased basal metabolic rate even to myxedematous levels, occasional Addisonianism, and decreased hair in the sex-influenced areas of hair distribution.

4. *Diabetes insipidus and adiposity.* These occur as signs of the effects of compression on the posterior pituitary and/or hypothalamus.

5. *Lethargy and personality changes.* In the absence of secondary hypothyroidism and hypogonadism, loss of mental and physical vigor, coupled with other changes such as memory or neurologic defects, reflect the pressure effects on the hypothalamus, and on the temporal and frontal lobes inferiorly in the cases of the largest adenomas.[1]

6. *Changes in the chemistry of blood and urine.* These reflect the endocrine changes of the hypophysis and its target-glands.[2]

Treatment Methods

The approach to treatment of chromophobe adenomas must be conditioned by, (1) the presenting symptoms, and (2) the rate of progress of symptoms, especially of the visual symptoms. Therefore, we believe *surgical* treatment is indicated for the adenoma which is rapidly expanding due to intracapsular hemorrhage or to rapid cellular growth, acutely threatening vision and/or life, and also in instances where there is strong suspicion of a cystic lesion, or when the clinical diagnosis is uncertain. *Radiotherapy* should be used postoperatively in the surgically treated cases, and in the cases presenting classical diagnostic signs of adenoma but without previous surgical treatment. *Endocrinologic* support should be provided for those who display endocrine dysfunction as the result of radiotherapy used for suppression of the adenoma itself. These concepts appear to be fairly well accepted

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by the more recent investigators of this problem.[3,4]

The need for radiation therapy of chromophobe adenomas has been adequately established and documented by many earlier studies. Our concern is to attempt an evaluation of the results of planned single-course x-ray therapy in tumor doses of about 4,000 r, as advocated by Buschke among others.[5,6] In so doing, we have available data for patients treated with "low dosage" (2,240 to 3,460 r), and those with "adequate dosage" (about 4,000 r), with and without pre-irradiation surgery.

We are considering here results of treatment only in terms of improvement of symptoms, whether visual (the most important, usually), headache, "hypothalamic" or endocrine. The patients who initially complained of headache and visual impairment, and who showed improvement in vision after treatment also claimed improvement in, or disappearance of headache. Thus far our follow-up period is not long enough for conclusive data on recurrences, a consideration we expect to discuss after five or more additional years of observation. Thus far 4 patients have had recurrent symptoms after initial improvement; they were all in the "low dosage" group. We hope that the increased percentage of improvement following "adequate dosage" x-ray therapy will continue to be reflected in a significantly lower recurrence rate. For the purposes of this report we have tabulated as "improved" those patients who have had objective remissions of symptoms for not less than 6 months after the end of treatment and with no recurrence during the span of observation to date. Actually, only one patient has had as little as 6 months observation, and only 3 patients less than 2 years observation.

TABLE 1

CASES OF CHROMOPHOBE ADENOMAS

(The University of Texas Medical Branch Hospitals, 1945-1956)

Total recorded cases		35
Planned x-ray therapy	26	
No x-ray therapy course	9	
Surgery		17
Pre-irradiation	14	
Alone (postoperative deaths)	3	
Not evaluated		2
Now being treated	1	
Died before treatment	1	

TABLE 2

RESULTS OF TREATMENT IN 35 PATIENTS HAVING CHROMOPHOBE ADENOMA

Planned course x-ray therapy	26	
Improved		18 of 26 = 70%
"Low dose" cases		4 of 10 = 40%
"Adequate dose" cases		14 of 16 = 88%
No x-ray therapy	9	
Left hospital A.O.R.		2
Post-ventriculogram death		1
Post-craniotomy death		3
Postmortem incidental finding (microscopic)		3

Results

Table 1 represents the case material in this series. It is noteworthy that operation preceded radiation therapy in 14 of 26 patients who received a planned course of x-ray treatment. Surgery was not employed as the sole method of treatment; the 3 postoperative deaths of course excluded any use of radiation for those patients. One patient who died immediately after a ventriculography has been excluded from the series since no treatment was given.

In table 2, we have summarized the results of x-ray therapy without regard to factors other than the groupings related to tumor dose. The difference between the "low dosage" and "adequate dosage" improvement rates, 40 per cent and 88 per cent respectively, is dramatic and significant. It supports our continuing investigation of this factor in treatment.

There were 3 patients who received no irradiation and are not considered in this evaluation; they were diagnosed at postmortem by microscopic examination, and had died from unrelated causes.[7] The death rate after craniotomy is in keeping with the experience at other centers, and we must recognize that it

TABLE 3

THE INFLUENCE OF TREATMENT METHODS ON RESULTS IN 26 TREATED CASES OF CHROMOPHOBE ADENOMA

Treatment method	*Improved*
X-ray therapy only	7 of 12 = 58%
"Adequate dose"	5 of 6 = 84%
"Low dose"	2 of 6 = 33%
Surgery* + x-ray therapy	11 of 14 = 79%
With "adequate dose"	9 of 10 = 90%
With "low dose"	2 of 4 = 50%

*Three postoperative deaths are not included, because we are evaluating treatment policy, which does not include surgery alone.

reflects, to some degree, some unfavorable cases included in the group operated upon.

The question of the influence of surgical treatment before irradiation on the results is considered in table 3. We find that 12 patients had no operation before x-ray therapy; 14 patients had a craniotomy for diagnosis or decompression. In both groups improvement was shown in approximately equal percentages (84 and 90 per cent), for the "adequate dosage" cases, and at considerably higher rates than in the "low dosage" groups.

It would obviously be misleading to evaluate the factor of radiation therapy alone or in combination with surgery, without taking in account the adequacy or inadequacy of the radiation dosage. From the foregoing data we suggest that the use of an adequate x-radiation technic is a more significant factor in affecting improvement rates than is the employment of surgical treatment before irradiation. Again, however, we must bear in mind the necessity for craniotomy in the special circumstances noted in a previous paragraph.

Technic of Radiation Therapy

For those patients treated to the higher tumor-dose levels of 3,800 to 4,500 r, we employ right and left temporal, frontal and superior (vertex) fields with the central x-ray beam directed to the sella turcica and, if where indicated, suprasellar region. For lower doses, 3 fields are sufficient. Fields are small, usually 25 sq. cm. and never larger than 50 sq. cm. now. Physical factors have not varied to a significant degree as x-ray apparatus has changed: 200 or 250 kv., 20 or 30 ma., half value layer 1.2 to 4.0 Cu., 50 cm. T.S.D. Inasmuch as treatment is started cautiously, often at low initial daily doses, an over-all time of about 40 days is usually required in order to accomplish a minimal tumor dose of 4,000 r, our present goal. All available evidence indicates that such dosage is safe for the adult brain, especially with the use of small fields.

Diagnostic radiographic aids, such as cerebral angiography and intracranial air study (usually pneumoencephalography), are used when indicated and often yield useful information about the extent of suprasellar or parasellar tumor growth. For localization and beam-direction, we may use fluoroscopy for the lateral fields, portal flash-films routinely, and beam-directing attachments to our apparatus.

Epilation of the vertex and lateral fields occurs regularly, but temporarily; there has been regrowth of hair in all our cases, in a period of 2 to 6 months. Each patient has determinations of visual field and acuity, by a neurosurgeon or ophthalmologist, immediately before x-ray treatment is instituted. Follow-up examinations are most informative as a joint effort with our colleagues, and include pertinent visual, neurologic and laboratory studies in each case.

Summary

1. Thirty-five cases of chromophobe adenoma, recorded between 1945 and 1956, have been studied.

2. Of this group, 26 were treated completely.

3. The effects of x-ray dosage and of surgical treatment before irradiation are evaluated in terms of clinical improvement.

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The Management of Inoperable Cancer of the Prostate*

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The author presents his views as to the optimal time to use castration and/or estrogen therapy in the management of inoperable prostatic carcinoma.

THE PRINCIPAL OBJECTIVE of this paper is an attempt to counteract as much as possible the decrease in life expectancy accompanying the management of so-called inoperable cancer of the prostate. Another objective is to present the various forms of management in the hope of extending life expectancy with as little physical discomfort as possible.

It is my opinion that the use of any type of endocrine therapy before a patient with inoperable prostatic cancer has pain or is showing an unsatisfactory clinical trend destroys life expectancy. This is difficult to prove and I cannot prove it with my case records because I have not felt I could conscientiously manage any patient in this way. The best statistical study appears in this table from Flocks.[1]

In this table I would like to call attention to the 43 per cent of the 5 year survival group who had transurethral resection and stilbestrol later, as compared with 23 per cent who had stilbestrol initially and then transurethral resection.

All of you know patients with prostatic cancer who had it for a number of years with no appreciable physical incapacity. It is in this group that the immediate institution of endocrine management constitutes the dissipation of our reserve control measures.

Let us discuss the various available methods which may be utilized in the management of inoperable cancer of the prostate patient.

First, one may use estrogen or castration. From data available it is difficult to determine which of these two policies is the better. There are several factors which may call for one or the other of these forms of therapy, depending upon,—the attitude of the patient, the degree of response to estrogenic therapy, the opinion of the internist with regard to operation, even at its present low risk. (I have one distinguished friend who always uses estrogen therapy first.) The dose of estrogen should be the smallest effective dose, beginning at 1 mg. of stilbestrol as a basic amount and then be increased to whatever is the effective amount. If estrogens are not effective castration should be carried out. Castration by x-ray, as described by Munger,[2] may be used in the few circumstances which make this type of castration advisable, though is not considered as satisfactory as the surgical. When either castration or estrogen therapy becomes ineffective then either of the other can be used next.

Cortisone, in doses of from 25 to 100 mg., sometimes gives spectacular relief when patients get out of control or when they have not responded to the aforementioned measures. Adrenalectomy is available in these patients and should be carried out when, and if the patient and his family understand the percentage of responses and would like to have it done. Since statistics have shown that adrenalectomy is followed by effective control for varying periods of time in about 20 per cent of patients, it seems he should be advised of this and if he wants or demands it the surgeon should afford it.

The relationship of pituitary to this problem has suggested various attacks on this gland. I first called attention to pituitary in radiation in 1942.[3] In recent years the pituitary has been irradiated by the implantation of radon seeds, or the injection of radioisotopes via the nasal route. Direct surgical removal of the pituitary gland has also been used. These measures also should be carried out only at the request of the patient or his family.

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Nitrogen mustard has, in one instance, been rather effective in controlling cancer of the prostate which had not responded to estrogens or castration.

The problem of general support is a most important aspect in the management of these patients. This means an adequate intake of vitamins and good nourishment, periodic blood transfusions if indicated, and a cheerful and encouraging attitude on the part of those who attend the patient.

Obstruction offers a mechanical problem separate and distinct from the cancer itself. Its relief may be by transurethral resection, retrograde suprapubic resection, suprapubic prostatic enucleation, or by perineal prostatectomy after preliminary preparation by the use of estrogen as described by Colston and Brendler.[4] Each procedure has its indication.

Deep irradiation by the x-ray of the prostate itself is at times a most successful and effective method of treatment for the relief of obstruction and control of growth. The radium needle which was used for sometime is now quite generally discarded. The injection of radioactive gold into the prostatic cancer tissue itself, as described by Flocks[5] has been spectacularly effective in his hands, and in those of a few others.

In inoperable cancer of the prostate the problems are individual, and since there are so many different ways of management available one should take time to appraise the reason for employing one or another of these methods.

The variability of the clinical course may be most confounding in prostatic carcinoma since the cancer cell by no means acts the same in every patient. Until one can explain why administration of estrogen, castration, or removal of the adrenal or the pituitary, will or will not favorably influence these cancers there will be no answer to these matters.

The enzyme determinations are unsatisfactory in assisting in early diagnosis and in indicating the clinical course in the patients.

Conclusions

1. The policy of using castration or estrogens as soon as the diagnosis of inoperable cancer of the prostate is made is probably destroying many years of potential extension of life.

2. Neither castration nor estrogens should be used until the patient is having pain from metastases or the clinical course is unsatisfactory.

3. If obstruction is the major problem it can be managed by other means than endocrine treatment.

4. We are patiently looking forward to the time when we will understand and control the vital factors involved in the inhibition or stimulation of the malignant prostatic cancer cell.

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Discussion (Abstract)

Dr. William Wallace Scott, Baltimore, Md. I have enjoyed Dr. Herbst's paper very much. He is one of the pioneers in the endocrine control of prostatic cancer, and since the early 1940's I have followed his publications with interest.

In the early 1940's it became clear that the response to castration-estrogen therapy varied. Roughly one-third of the patients responded well for long periods of time, one-third for periods ranging from 6 to 18 months, and one-third failed to respond.

In 1950, Nesbit and Baum, of the University of Michigan, were commissioned to pool the collected cases of a group of urologists representing a cross section of standard urologic practice in North America. For standardization, the data were collected on a prescribed printed form and only those cases were used in which diagnosis was a certainty through microscopic examination of tissue, or laboratory and x-ray examinations confirming the clinical diagnosis by competent urologists. Treatment consisted of castration alone, estrogen administration alone (1-5 mg. of diethylstilbestrol, or its equivalent), or a combination of the two. The three treatment groups were subdivided on the basis of presence or absence of metastases to lymph nodes or bone at the time treatment was begun.

Though most of you are familiar with these data, I wish to show by a slide what the 5 year survivals were without demonstrable metastases when treatment was begun. Combined therapy (i.e., castration-estrogen) proved most effective and significantly more so than castration alone or estrogen alone. The other slide presents the 5 year survivals of those who had demonstrable metastases when treatment was begun. These faired less well, approximately 20 per cent surviving 5 years. Castration alone, or combined with estrogen therapy, appeared to be more effective than estrogen administration alone.

When 213 patients, originally treated with one form of therapy alone, were treated for relapse with the other form, symptomatic relief was reported in 36 per cent. The period of subsequent remission and survival was about the same in the groups treated for relapse by estrogen and by castration. On the average these patients survived only 9 to 10 months after the onset of relapse.

In my opinion, this study of Nesbit and Baum does not permit one to deduce the optimum time to initiate endocrine therapy. Regarding this point I am of the same opinion as Dr. Herbst, namely, that endocrine therapy should be reserved until the time when the patient with metastases is having pain, weight loss, etc. I also agree that these patients should receive careful medical attention, not necessarily of a specific hormonal nature.

Although I have resorted to bilateral adrenalectomy and hypophysectomy in the treatment of relapse, the indications for either are not sufficiently clear for discussion. Rather, I wish to describe briefly work in progress in our laboratory directed toward predicting response and relapse based on careful measurement of certain urinary steroids. The methods in use permit us to measure "androgen" metabolites, derived from both the testes and the adrenal, and "corticoid" metabolites, derived from the adrenal only.

We believe that the object of therapy in inoperable prostatic cancer is to lower the patient's androgen production, thus tests which measure "androgen" metabolites in the urine may be an objective way of following a patient's response to therapy. Also, such measurements may dictate the therapy to be used. The two "androgen" metabolites which we measure in the urine are *androsterone* and *etiocholanolone*. The former is a biologically active androgen; the latter is inactive. Both are derived from testosterone (possibly from 17-hydroxycorticosterone in the absence of the testes). For purposes of reporting we have set up a ratio of androsterone to etiocholanolone, (A-E ratio), and it is reasonable to believe that the higher this ratio, the greater the production of androgens by the testes and the adrenal, and the lower the ratio the lower the production. This slide shows results in 10 patients carefully studied for periods up to 18 months, both before and after treatment. Treatment of one form or another, i.e., castration or estrogen administration, has not been altered unless the patient has relapsed on one or the other. Examination of the columns labelled *"ratio"* and *"present state"* reveals that the patients who did poorly and relapsed produced a higher percentage of "androgenic" androsterone in relationship to physiologically "neutral" etiocholanolone.

To date, one patient who relapsed on castration-estrogen therapy showed a dramatic fall in his A-E ratio when he received 100 mg. of cortisone daily. He improved clinically. Fifty mg. per day was not effective in lowering his A-E ratio, nor did it give him any relief.

During the course of the next 6 to 12 months we propose to carry out adrenalectomy and hypophysectomy in a few selected cases. For example, we will be interested to learn the results of adrenalectomy in a patient whose A-E ratio is high after castration-estrogen therapy. Such a patient should receive benefit.

Two additional points of interest: (1) The administration of chorionic gonadotropin has no effect on steroid levels in the castrate patient. (2) ACTH given after castration causes a rise in both "corticoid" and "androgen" metabolites. These observations suggest that attention should be directed toward inhibiting ACTH production or its release in order to diminish "androgen" production in the castrate.

As a clinician faced with the care of the patient with prostatic cancer, I hesitate to sit down without making a plea for the early recognition, and early surgical treatment of prostatic cancer. Cures can be effected by no other means. Hormonal therapy is only palliative. I may summarize what I believe is important in the diagnosis and treatment of prostatic cancer: (1) prostatic cancer is a common cancer; (2) in its early stages, prostatic cancer causes few symptoms, and we must rely on routine rectal examinations for early diagnosis; (3) all hard nodules felt in the prostate gland on rectal examination should be considered cancers until proved otherwise; (4) surgical biopsy is the only reliable means of establishing a diagnosis of prostatic cancer; and (5) total prostatectomy is the only means of affecting a cure.

CASE REPORT

Acute Occlusions in the Renal Vascular Pedicle: A Case Report of Acute Thrombosis of the Renal Artery*

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ACUTE THROMBOSIS of the renal artery and acute thrombosis of the renal vein are relatively rare lesions. However, both of these vascular catastrophies are undoubtedly more common than is recorded in the literature. Many of the reported cases have not been diagnosed preoperatively;[1] in fact, it was not until 1942 that Campbell and Matthews[2] made the first preoperative diagnosis of massive unilateral thrombosis of the renal vein which was subsequently cured by nephrectomy. The paucity of cases reported in the literature, the difficulty in establishing a preoperative diagnosis, and the general unfamiliarity with acute renal infarctions warrants the report of the following case.

Case Report

This 68 year old male patient was admitted to the hospital on October 30, 1955, and subsequently discharged on December 12, 1955.

History. The patient stated that he was well until the evening of October 30, 1955, at which time he noted the sudden onset of excruciating low back pain. The pain subsequently radiated to involve the entire anterior abdominal wall and chest regions. He described the pain as being so severe that he felt as if he would faint. His family physician examined him and gave him 100 mg. of Demerol intravenously in an effort to relieve his pain. The Demerol had little effect upon his pain and he was admitted to the hospital for further evaluation.

Past History. In 1956, he had an episode of hematemesis, and again in 1950 he vomited bright red blood on three occasions. A radiologic diagnosis of bleeding duodenal ulcer was made. In 1946, his physician reported that his blood pressure was "slightly" elevated, but more recently blood pressure determinations were reported as normal.

Physical Examination. This revealed a well developed, slightly obese white man who was writhing in bed with pain. His blood pressure was 220/140, pulse 76 per minute, temperature 98°. The lungs were normal. A grade I systolic murmur was heard at the aortic area. Examination of the abdomen did not reveal distension or visible peristaltic waves. Generalized abdominal tenderness was present; however, the tenderness was more pronounced on the right side of the abdomen and in the right costovertebral angle. True muscle spasm and direct rebound tenderness were present in the right lower quadrant. Bowel sounds were hypoactive. Rectal examination demonstrated tenderness high on the right anterior rectal wall. Femoral pulses were equal; the right dorsalis pedis pulse was diminished as compared to the left.

Laboratory Examinations. Red cell count was 4,500,000, Hgb. 16 Gm., white cell count 18,050 with the differential count showing 87 per cent of polys. Urine was normal. Serum amylase was 134 units per cent. Clotting time was 8.5 minutes. Six hours following admission the urine showed 3 + albumin, 2 to 4 RBC and 1 to 3 WBC per HPF, and an occasional granular cast. The white count and differential were essentially unchanged.

Chest x-ray films showed tortuosity and slight widening of the thoracic aorta, and enlargement of the left ventricle. Plain film and upright x-ray examinations of the abdomen were normal. Intravenous pyelograms revealed nonvisualization of the right collecting system; the left upper collecting system was normal. Cystoscopic examination and retrograde pyelograms were reported (M.F.F.) as follows: "The findings are those of a normal retrograde pyelogram on the right with suppression of urine from the right kidney."

Operation. An exploratory celiotomy was carried out. The right renal artery was thrombosed and the right kidney showed the typical picture of pale infarction. The right kidney was excised and following removal of this kidney the patient's blood pressure dropped to 90/40. A transfusion of 1,000 cc. of blood was given with immediate elevation of the blood pressure to 120/60 to 130/60.

For the next five days his blood pressure was extremely unstable and it was necessary to give a constant drip of *l*-norepinephrine to maintain his pressure at an

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adequate level. His urinary output for the first two days postoperatively was 300 and 400 cc. respectively. Subsequently his output was 800 to 1,400 cc. daily. Careful control of his fluid and electrolyte balance was maintained. The day following operation he was digitalized because of cardiac failure. Heparin and Dicumarol were started in an effort to prevent further thrombotic episodes. On the third postoperative day the patient became quite restless and all efforts to prevent subcutaneous extravasation of *l*-norepinephrine failed. At the time extravasation occurred the patient went into profound shock, and shortly after restoring his blood pressure to 130/70 with intravenous *l*-norepinephrine, he developed pulmonary edema which responded to intensive treatment. Subsequently it was necessary to excise the slough on the left leg and graft the area with a split thickness skin. Following this procedure his course was one of progressive improvement. Twelve months following his discharge from the hospital his blood pressure was 130/80 and the urine examination was normal.

Pathology Report. The sections of kidney show an extensive degree of cortical necrosis. A mild degree of nephrosclerosis is noted in the uninvolved parenchyma. The main renal artery shows marked atherosclerosis with a large thrombus completely occluding its lumen.

Diagnosis. Infarction of the kidney secondary to renal artery thrombosis.

Comments. This patient presented the typical picture of acute unilateral renal artery thrombosis. Several diagnostic possibilities were considered: perforated duodenal ulcer, acute pancreatitis, appendicitis, dissecting aneurysm, and acute thrombosis of the right renal artery. Several patients with acute thrombosis of the renal artery have been reported in whom an exploratory laparotomy was carried out for suspected acute intra-abdominal surgical lesions.[3]

Adequate base-line blood pressure determinations are not available. At the onset of his illness, the family physician recorded the blood pressure at 120/80. Assuming that this represents his usual blood pressure, one can see that a rapid hypertension may develop in these patients. Goldblatt[4] has shown that complete renal artery occlusion will not produce hypertension. It is postulated that enough arterial blood reached the kidney via small accessory arteries and through the capsular collateral circulation to duplicate the "Goldblatt phenomenon." The prompt fall of the systolic and diastolic pressure to normal levels, and the persistence at normal level for twelve months would certainly seem to incriminate the renal artery thrombosis as the cause of his acute hypertension.

The shock which occurred following nephrectomy might be explained as "withdrawal shock" which is known to occur after excision of a pheochromocytoma and after sudden discontinuance of an intravenous drip of *l*-norepinephrine. Perhaps the vascular tree becomes "addicted" to the pressor agent and sudden withdrawal produces vascular collapse. Treating vascular collapse and simultaneous pulmonary edema is a frustrating problem. Application of limb tourniquets, aminophylline intravenously plus increasing the concentration of *l*-norepinephrine to allow a decrease in the rate of the intravenous infusion was helpful in this patient. Sloughs produced by extravasation of *l*-norepinephrine are most distressing. These sloughs are usually quite deep, with necrosis of the skin, subcutaneous tissues, fascia and muscle occurring not uncommonly. Early excision of the slough and split thickness skin grafting was carried out successfully in this patient.

TABLE 1

ACUTE RENAL VASCULAR OCCLUSIONS

Acute Arterial Thrombosis	*Acute Venous Thrombosis*
1. Sudden onset of severe flank or upper abdominal pain	1. Sudden onset of flank or upper abdominal pain,—not as severe as acute arterial thrombosis
2. Geriatric age group, or patient with cardiac disease	2. Neonatal period, usually with associated septic state
3. Predilection for males	3. Occurs equally in both sexes
4. Evidence of unilateral peritoneal irritation	4. Evidence of unilateral peritoneal irritation plus palpable tender mass
5. Hypertension may develop early or late	5. Hemorrhages may occur
6. Urine findings may be negligible, albuminuria and hematuria may be present	6. Urinary findings may be negligible, albuminuria and hematuria may be present
7. Oliguria may or may not occur	7. Oliguria may or may not occur
8. I.V.P.'s—nonvisualization of involved collecting system. No enlargement of renal shadow	8. I.V.P.'s may show distortion or incomplete filling of upper collecting system. Enlarged indistinct renal shadow
9. Cystoscopic examination—little or no urine from involved ureter. Absence of indigo-carmine dye excretion by involved ureter	9. Cystoscopic examination,—little or no urine from involved ureter. Absence of indigo-carmine dye excretion by involved ureter
10. Retrograde pyelograms are normal	10. Retrograde pyelograms may show distortion of upper collecting system
11. Pale infarction, shrunken kidney noted at operation	11. Hemorrhagic infarction, enlarged cyanotic kidney with perirenal hemorrhage noted at operation

Discussion

Regan and Crabtree,[5] in 1948, clearly defined the differential features of acute massive renal vein thrombosis and acute renal artery thrombosis (Table 1). This summarizes the characteristic findings in these two disorders as well as the differential features.

The etiology of massive thrombosis of the renal vein is still obscure.[5] The majority of cases are seen in the neonatal period.[6] Usually the infants are dehydrated and have a septic disease, frequently epidemic diarrhea. The infection is almost invariably outside the urinary tract which had led to many hypotheses as to the cause of renal vein thrombosis,—changes in the concentration of the coagulating mechanisms, local congenital abnormalities of the venous endothelium, and toxic effects on the venous endothelium secondary to infection. Other causative factors have been cited on various occasions,—infection in and about the renal vein, extension of a thrombus in the vena cava, invasion of the renal vein by neoplasm, amyloidosis, trauma and thrombophlebitis migrans.[7]

The most common causes of acute occlusion of the renal artery are: thrombo-embolic disease secondary to various types of heart disease, local atherosclerosis with ulceration plus superimposed acute thrombosis, invasive infection about the renal artery, neoplastic infiltration of the renal artery, acute thrombosis of an aneurysm of the renal artery,[8,9] Leriche's syndrome with extension of the thrombus to involve the renal artery, and toxemia produced by a fulminating infection.

There is a general agreement that early diagnosis followed by nephrectomy is the treatment of choice for acute thrombosis of the renal vein.[5,6] The use of anticoagulants postoperatively may have merit and should be used unless specific contraindications are present. The possibilities that massive unilateral thrombosis of the renal vein will progress via the vena cava to involve the opposite kidney is real and can be avoided by removing the damaged kidney. If the picture is one of bilateral thrombosis of the renal vein, the prognosis is extremely grave. In these cases one must use a rapidly acting anticoagulant in an effort to save the patient's life. The use of blood transfusions and broad spectrum antibiotic coverage are essential in preventing shock and infection.

Since occlusion of one of the major branches of the renal artery usually produces the same clinical picture as complete occlusion of the main renal artery, conservative management with anticoagulants, careful control of fluid and electrolyte balance, antibiotics, and analgesics, is the treatment of choice.[5] The infarcted kidney, or segment of the kidney, usually undergoes aseptic necrosis without complications. Relief of the excruciating pain in these patients is a real problem. Blockage of the sympathetic nerves with 1 per cent procaine may be helpful. One might speculate that if the diagnosis of acute thrombosis of the main renal artery could be made early an effort to restore continuity of the vessel might be attempted. Hypertension caused by complete or partial occlusions of the renal artery are being reported more frequently.[9] This possibility should be ruled out in all patients with essential hypertension.

Summary

Acute thrombosis of the renal artery and acute thrombosis of the renal vein can be diagnosed early if these vascular catastrophies are kept in mind. Massive thrombosis of the renal vein most frequently occurs in the neonatal period, usually associated with epidemic diarrhea, and if unilateral is best treated by emergency nephrectomy. Acute thrombosis of the renal artery occurs in patients who have cardiovascular disease, and since one cannot differentiate between partial and complete renal infarction, conservative management is the treatment of choice. If one makes a diagnosis of an acute surgical abdomen, and no disease is found at celiotomy, the renal vascular pedicle should be palpated for evidence of thrombosis.

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Physical Therapy in Lesions of the Intervertebral Disk of the Lower Back*

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The author outlines a simple conservative plan of treatment for the syndrome of disease of the intervertebral disk.

AN INCREASING NUMBER OF PATIENTS with lesions of the intervertebral disk of the back are finding their way into the office of the physiatrist, chiefly because recently there has been a greater emphasis on the conservative management of these cases.[1]

The question arises,—what is the best treatment we can offer these patients? Obviously the best treatment is that designed to counteract the anatomic, physiologic, and mechanical derangement produced by the disk lesion. The basic anatomic disturbance responsible for the patient's symptoms is the alteration of the shape and size of the neural canal and the intervertebral foramen through which the spinal nerves reach the periphery from the spinal cord.

The neural canal is formed by the vertebrae above and below with the intervertebral disk holding the vertebrae apart. Lesions involving the disk cause narrowing of the neural canal, a decrease in the size of the intervertebral foramen, and results in compression of its contents which consists of the nerve root, blood vessels, and soft tissue.

Studies of effects of pressure on spinal nerves[2] have shown that in mild compression the nerve becomes hyperirritable and ischemic but the axons are intact. Pain becomes a dominant symptom and is probably due to ischemia rather than to pressure on nerve fibers. The hyperirritability of the compressed and ischemic nerve roots results in muscle spasm involving most frequently the paravertebral muscles. The muscle spasm causes more pain which keeps the spine extended, lessening further the capacity of the neural canal and foramen.

It then follows logically that relaxation of the spastic muscles, relief of ischemia, and mechanical means of relieving pressure on the nerve roots are rational measures in the management of this condition. To accomplish this the following routine is carried out in the office:

1. *Heat.* Short-wave or microwave diathermy, or infrared radiation is given for about twenty minutes. It relaxes the muscle spasm and increases the blood supply to the area.

2. *Histamine by Ion Transfer.* Imadyl Unction is applied over the involved area. A wet cloth and the active electrode are placed over it. The larger inactive electrode is placed on the patient's abdomen (trans-application). The active electrode is connected to the positive pole of a direct current source and about 7 to 8 milliamperes of current is passed for about 5 to 7 minutes, or until the patient develops a mild flushing of the face. Histamine is an effective vasodilator.[3] It relaxes spastic muscles and has a marked analgesic effect on muscle and nerve tissue. Occasionally the patient will complain of a headache. This is controlled through the administration of an antihistamine tablet. Histamine is not used when the patient gives a history of asthma or hay fever.

3. *Ultrasound.* While the exact mode of action of ultrasound or neural tissue is not known, its successful application in painful neuritic conditions is found in the medical literature.[4] It has been postulated that the analgesic effects on neural tissue and nerve endings are the result of heat and mechanical vibrations. Some claim that mechanical massage can move fluids along the course of a nerve trunk, thus causing the disappearance of painful sensations. The sound head is moved over the paravertebral area close to,

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but not over the spinal column and over the sacro-iliac junction. Duration of treatment is 5 to 7 minutes using 1.5 to 2.5 watts per square centimeter.

4. *Flexion Exercises.* It has been well established that flexion of the spine increases the size of the intervertebral foramen and neural canal and extension narrows it.[5] Flexion produces stretching of the tense paravertebral muscles and ligaments. The following 3 simple flexion exercises are carried out in the office and twice daily at home.

(a) The patient is supine on the treatment table. He flexes the thigh at the hip and the leg at the knee on the normal side. He grasps the leg just below the knee with both hands and approximates the thigh to the abdomen. He does this maneuver on the involved side several times.

(b) The patient is supine on the treatment table. A rolled blanket is placed under the knees to neutralize tension on the hamstring muscles. The patient is instructed to come gradually to a sitting position and bend forward as if attempting to touch his toes with his outstretched hands. The physician grasps the patient's hands and pulls him gently and steadily forward compatible with the patient's tolerance for pain. This is done 3 to 4 times. Then he pulls the patient to the right and left of the midline a couple of times.

(c) The patient sits on the treatment table or on a chair with his knees fairly close together. He bends forward and attempts to touch his toes with his upper extremities, skirting the tops of his knees. He then does the same exercise with his upper extremities pointing to the right and left in relation to his knees.

This office treatment of a sequence of heat, histamine by ion transfer, ultrasound, and flexion exercise is given 2 or 3 times weekly. It has proven highly successful in eliminating the patient's symptoms in all types of lesions of the intervertebral disks. Unfortunately these clinical results are not backed up at this time with statistical and controlled studies. Nevertheless the clinical results have been so uniformly good that they justify the assertion that no one can say that he has given the patient the benefit of conservative management until the above treatment has been carried out for at least six sessions.

Summary

1. The salient features of the anatomic and mechanical derangement in lesions of the intervertebral disk have been given.

2. A rational sequence of physical therapeutic measures for treatment has been outlined.

3. This treatment has been found highly successful in eliminating symptoms.

4. It is recommended that treatment consisting of heat, histamine by ion transfer, ultrasound, and flexion exercise be used in all cases of this syndrome where conservative management or its trial is desired.

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Discussion (Abstract)

Dr. Charles Stansky, Bay Pines, Fla. The contributions that the physiatrist can make to the proper handling of the patient having a lesion of the intervertebral disk are indeed many. It is important to recognize that the herniated disk involves not only the spine, but also the roots of important nerves supplying the muscular system. His soma and his ego are dramatically threatened, and naturally a sense of insecurity with resulting anxiety develop! The physiatrist must have at his command different modalities of physical therapy for this type of patient. He should be able to change from one to the other until he finds the modality most effective. Workers in the field of conservative therapy for such patients are usually surprised that the manipulation of the lumbosacral spine which would appear most logical, in attempting to reduce the herniated disk, has usually been found disappointing. Therefore, this paper describing the different modalities of physical therapy to be used discriminately and effectively for these patients is important.

About 90 per cent of such patients who present themselves to any large Physical Medicine Service are aided by efficient conservative management. The first procedure a patient with low back pain undergoes at our clinic is a thorough history and physical examination. His x-ray films are studied. We attempt to establish good rapport with our patient.

Where muscle spasm of the lumbar and erector spinae muscle groups is most prominent, luminous infrared or deep penetrating short wave diathermy is prescribed and is usually found effective in easing the patient. Where the irritation of the sciatic nerve is for the most part the cause of the patient's discomfort, ultrasonic therapy may be the modality most useful. The therapist is instructed to give these treatments with the patient either in a sitting position with his head resting on a table or in a lateral position on a table with the lumbosacral spine flexed as much as possible. Investigators have found that with the lumbosacral spine flexed anteriorly as much as possible the intervertebral foramina are expanded as much as is possible and pressure on nerve roots may in this manner be eased.

In our clinic we found anterior flexion exercises of the lumbosacral spine a very effective method in helping the patient with the disk syndrome. However, during the acute phases of low back pain due to a herniated disk physical therapy such as luminous infrared and short wave diathermy with sedative massage may be all that is prescribed. But as his discomfort leaves the exercises are introduced. He receives treatment twice a day when the condition is severe. As he improves a lumbosacral support is prescribed for him and the patient is given a more active exercise program. He is taught that he has to live with his disability. The proper positioning when he gets to bed for his night's rest is stressed. His exercises must be followed religiously, in the morning on getting up, and at night before retiring.

For the patient with severe disease of the disk, a change in occupation is very often part of his rehabilitation program.

In closing, let me reiterate that most physiatrists and orthopedists are agreed that about 90 per cent of patients with herniated intervertebral disks are benefited by well-planned programs of conservative therapy, which for the most part consist of physical therapy modalities and therapeutic exercises.

Chloranil in the Treatment of Psoriasis: A Substitute for Chrysarobin*

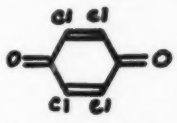
WALTER O. TEICHMANN, M.D., and
PETER N. HORVATH, M.D., *Washington, D. C.*

The authors offer a new agent which seems to be effective in the treatment of a vexing cutaneous lesion.

THE FUNGICIDAL PROPERTIES of chloranil (tetrachloro p-benzoquinone) have been extensively studied by McGavack and associates,[1] Rankin and collaborators,[2] Moore,[3] Gordon,[4] and by Collins, McGavack and Boyd.[5] During the use of this material in an instance of tinea capitis infection accompanied by psoriasis, it was observed that the psoriasis resolved during the treatment of the fungal infection. This observation has been extended to other cases of psoriasis and the present paper details our experience with chloranil in the treatment of 93 such cases over a period of two years.

Material and Method

Chloranil is a bright yellow powder having the following formula. It is insoluble in water, but it is slightly soluble in the polyethylene glycols which makes these materials particularly effective as carriers. Chloranil was incorporated in polyethylene glycol-1500 in concentrations of 5 and 10 per cent.** The patients were instructed to apply the ointment thinly at bedtime, and to rub it in very thoroughly so that no excess remained. Chloranil stains the skin a light brown which usually is not troublesome, but if desired may be removed by wiping with a fat solvent such as petroleum benzin.



Results

The process of resolution is very similar to that of chrysarobin or coal tar therapy. The lesions first lose their scales, become less elevated and, in the most responsive cases, finally break up into small areas and fade away. The most marked improvement occurs during the first month. In several cases the lesions retrogressed when the treatment was stopped, and improved again on reapplication of the drug. No post-treatment leukoderma was observed.

The clinical appearance of the lesions was rated according to the classification of "much improved," denoting at least a 50 per cent resolution of the lesion, and "improved" referring to any resolution up to 50 per cent (Table 1).

The length of the treatment extended primarily from two weeks to three months, although some cases required as much as eight months (Table 2).

Chloranil appears to be most effective against the typical psoriatic plaque characterized by heavy scales. Furthermore it appears to benefit both palmar and plantar plaques as well as intertriginous lesions and to be least effective against the small guttate lesions. A listing of the types of psoriasis treated with chloranil appears in table 3.

In 24 patients comparable lesions in the same patients were selected for control studies, and were treated in the same manner with the carrier as with the chloranil formulation. In 10 of these patients there was no improvement; in 12 there was slight improvement although not equivalent to that of the areas treated with chloranil, and in 2 the improvement was equivalent to the areas treated with chloranil.

The 4 instances of worsened disease listed in table 1 consist of one case of true sensitization and 3 cases of primary irritation. In the 3 instances of primary irritation, this was ob-

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**Keranil, Salem Pharmaceuticals, Naugatuck, Conn.

TABLE 1

SUMMARY OF CLINICAL RESULTS WITH CHLORANIL

Concentration	*Total Number of Cases*	*Much Improved*	*Improved*	*Unimproved*	*Aggravated*
10%	63	39	14	6	4
5%	30	16	10	4	0

TABLE 2

DURATION OF TREATMENT

Number of Cases	14	24	18	14	9	3	7	4
Duration (weeks and months)	2 wks.	1 mo.	2 mos.	3 mos.	4 mos.	5 mos.	6 mos.	8 mos.

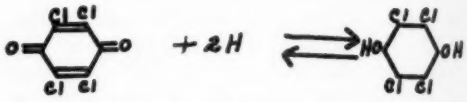
served with the 10 per cent but not with the 5 per cent formula.

Discussion

Until the pathogenesis of psoriasis is elucidated, the action of chloranil must remain empirical. It may be that the quinone nucleus is the locus of activity, and this finds support in that several of the components of chrysarobin such as emodin and chrysophanic acid are quinone derivatives. In this connection it should be pointed out that chrysarobin, a natural product, is of variable composition while chloranil being a chemical entity is of fixed composition.

In our opinion the antipsoriatic effect of chloranil approaches that of chrysarobin and is substantially free of the irritations and sensitization so frequently encountered with chrysarobin therapy.

It may be that an oxidizing agent is required and chloranil being a quinone is an oxidizer. Gans[6] has speculated that psoriasis might result from a disturbance in the oxygen metabolism of the skin. Ingram[7] has observed that the most effective local treatment involves the use of oxidizing agents. It was therefore of interest to examine the reduced form of chloranil, tetrachloro hydroquinone. This compound was tried in 4 cases as a 10 per cent formula in polyethylene glycol-1500. In no case was there any improvement and in one instance there was aggravation of the lesions. In so far as this work has gone, it indicates that the oxidizing component of the system chloranil,



—tetrachloro hydroquinone is the active agent.

TABLE 3

TYPES OF PSORIASIS TREATED WITH CHLORANIL

	Total Number of Cases
Generalized	31
Palms and soles	7
Legs and feet	18
Scalp and ears	27
Groin	3
Neck	5
Vulva	2

Summary

Ninety-three patients exhibiting typical lesions of psoriasis vulgaris were treated topically with 5 and 10 per cent concentrations of chloranil in a polyethylene glycol carrier. Considerable improvement was observed in 55 cases, moderate improvement in 24 cases and no improvement in 10 cases. In 4 cases the lesions became aggravated, one representing a true instance of sensitization. Control areas generally showed no comparable improvement. The reduced form of chloranil, tetrachloro hydroquinone was ineffective.

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Discussion (Abstract)

Dr. S. F. Horne, Rocky Mount, N. C. The treatment of psoriasis remains one of the most important and difficult tasks confronting the physician, and the wide variety of seeming unrelated medicaments is evidence of the lack of specific therapy. In spite of a voluminous literature, only minor contributions to the therapy of psoriasis have been made since the introduction of roentgen therapy.

It seems, therefore, that special thanks should go to people such as Drs. Teichmann and Horvath who, in the face of great odds, continue to seek the answer for this vexing disease. Chloranil is certainly not "the answer," but it will probably find a place in our armamentarium for psoriasis. The results are impressive and, at least in 5 per cent concentration it appears relatively safe.

Indeed, it seems to be good to have something "new for psoriasis," because that is the question asked by so many patients. I find it impossible to disregard the patients faith in a drug and frequently discover that its effectiveness decreases as I lose my original enthusiasm for it.

I have enjoyed the paper and I am grateful to the writers for something new for my psoriatics.

Dr. E. J. Van Scott, Bethesda, Md. Dr. Teichmann and Dr. Horvath have re-emphasized an observation that oxidizing compounds exert beneficial effects on psoriasis whereas reducing compounds do not. This criterion of usefulness perhaps has a biochemical basis in the fact that a large portion of the sulfur in scales of psoriasis is found in the reduced state, as sulfhydryl. (Zingsheim, M.: Die Rolle freier Sulfhydryl-gruppen bei der Schuppenflechte, Deutsche med. Wchnschr. 77:1630, 1952; Van Scott, E. J., and Flesch, P.: Sulfhydryl Groups and Disulfide Linkages in Normal and Pathological Keratinization, A. M. A. Arch. Dermat. & Syph. 70:141, 1954.) The action of oxidizing compounds may be to oxidatively unite sulfhydryl groups into disulfide linkages, thereby promoting the formation of a more normal stratum corneum.

The ideal local therapy of psoriasis may come about when a compound is found which is both compatible with the metabolism of the epidermis and is an ideal oxidizing agent as well. Since the chemical formula of chloranil is known, the observations of Dr. Teichmann and Dr. Horvath may give valuable directional information in a search for such a compound. From this aspect their observations may have a significance other than that chloranil is a good substitute for chrysarobin.

Doctors in Public Life

When the country was young and bursting at its seams, doctors like others moved from one profession or business to another rather freely—medicine to law to agriculture then perhaps back to medicine. But among doctors in national politics, the most popular transition was from medicine to military duty as line officers, then back again to medicine. This tendency was pronounced during the Revolutionary War, continued through the War of 1812, and was not unusual in the Civil War, even though by that time there was a national awareness of the great value of military surgeons.

Henry M. Shaw of North Carolina, served two terms in the U. S. House of Representatives before the Civil War. But when the fighting started he showed up as a line colonel in the Confederate Army and was killed in action near New Bern, N. C.

Similar to his career was that of a contemporary, Graham Fitch of Indiana, who raised a regiment of volunteers for the North and led the men as colonel until wounds forced his retirement. A younger doctor in Virginia, Robert E. Withers, followed the same course; a major of infantry, then colonel, finally discharged "in consequence of numerous disabling wounds." After the war he served in the Senate, founded the Lynchburg, Va., News, was named consul at Hong Kong.

A generation earlier Solon Borland of Arkansas had done the same thing—practiced medicine until the fighting started in Mexican and Civil Wars, then led troops in battle. His Senate service came between the wars. Similarly John Bratton of South Carolina preferred fighting to doctoring; like Dr. Borland he had the rank of line brigadier general in the Confederate Army. He was a U. S. Senator after the reconstruction period.

In view of these cases, it is not unusual that two physicians who served in Congress also were selected as Secretary of War. One was Henry Dearborn of Massachusetts, line officer in the Revolutionary War, secretary of war for eight years under Washington, member of Congress, then senior major general in command of troops in the War of 1812. An earlier Secretary of War for Washington was James McHenry of Maryland, whose Revolutionary War record shows him as surgeon, secretary to Washington, member of Lafayette's staff. He had sat in the Continental Congress.—(From the A.M.A. Special Report 84-30, 1956.)

The Use of S-Factor of Liver Extract (Kutapressin) in Dermatology*

EDWIN E. BARKSDALE, M.D., *Washington, D. C.*

It seems that this substance aids in the symptomatic relief of a number of cutaneous diseases. How this is accomplished is as yet unknown.

Introduction

THIS IS A CLINICAL EVALUATION of the use of a cutaneous vasolonstrictor, Kutapressin,** in the treatment of various dermatologic disorders. It contains an active principle obtained from crude liver extract. Lee[1] found that Kutapressin causes contraction of the smooth muscle cells of the peripheral blood vessels and enhances the action of epinephrine on them. It is not a vitamin; some investigators have referred to it as the S-factor.

Holtman[2] using Kutapressin preoperatively in dental extractions reported it to be of value in the prevention of hemorrhage and postoperative pain. Harris and associates[3] reported that it had no effect on bleeding and clotting times. Marshall[4-7] reports favorably on the drug in the management of tissue edema, burns, Raynaud and Buerger's diseases, and in the treatment of keloids and other related skin conditions. Barrock[8] and Poole[9] have reported on its usefulness in the treatment of acne rosacea. Heywood[10] has found that it gives relief and hastens healing in sunburn.

Clinical Studies

This report is based on the use of Kutapressin in 711 patients with dermatologic disorders. It was conducted over a four year period. The drug was administered intramuscularly in doses of 2 cc. The average time interval between injections varied from one day to one week. To obtain the best results injections should be given twice weekly or more frequently. There have been no untoward reactions attributable to the drug. Discomfort at the site of injection, if any, is minimal.

Acne Vulgaris. Kutapressin was used in a series of 178 patients with acne vulgaris of varying degrees of severity. Most of them were over 18 years of age.

Reports of several studies indicate the value of this S-factor of crude liver extract in acne vulgaris. Burke and Knox[11,12] reported a series of 226 cases corroborating previously published clinical reports of its value as adjunctive therapy. Lubowe[13] reported it to be of value in cystic acne. Nierman[14] reported that Kutapressin was an effective drug in treating 22 cases of refractory cystic acne. Pensky and Goldberg[15] reported moderate to good improvement in 63 per cent of 52 private patients with refractory acne. Barksdale and associates,[16] in a preliminary report in 1953, felt it to be a valuable adjunct. Nierman[17] states that in his opinion "Kutapressin, if used in doses that are sufficient both in size and frequency, is an extremely valuable adjunct in acne therapy." He based his opinion on a recent evaluation of over 200 patients who were given 2 cc. injections varying from daily to thrice weekly. He concludes: "Certainly Kutapressin alone is not a cure-all for acne, which is a complex problem in an extremely complex age group; but there is no question in my mind that it is beneficial." Barrock[8] in reporting on a study of 118 patients with acne rosacea states that in conjunction with other indicated procedures Kutapressin appears to accelerate the improvement and reduce the period of treatment required.

In this series of cases Kutapressin was not used alone. It was added to a treatment routine consisting of ultra-violet light, one of the "acne lotions" locally, a low fat diet and vitamin A. Over a period of years I have found this regimen effective.

The patients were started on a schedule of office visits twice weekly. Ultra-violet light

*Read before the Section on Dermatology and Syphilology, Southern Medical Association, Fiftieth Annual Meeting, Washington, D. C., November 12-15, 1956.

**Supplied by Kremers-Urban Company, Milwaukee, Wis.

TABLE 1

ACNE VULGARIS (178 Cases)

	Cases		Treatment	
	Number	Per Cent	Average Number of Injections	Average Total Dose
Under Control	89	50.0	16.2	32.4 cc.
Improved	59	33.1	14.9	29.8 cc.
Treatment Failure	30	16.9	14.8	29.6 cc.

and 2 cc. of Kutapressin were given at every visit, and the patients were repeatedly cautioned to continue with their diets and topical applications.

Table 1 shows that after 16 injections 50 per cent of the 178 patients were brought "Under Control" to the extent that they were permitted to discontinue their office visits except in case of recurrence. They were impressed with the necessity of continuing with their diets and general skin care. The 33.1 per cent listed under "Improved" represent an improvement of 50 per cent or better. There was "Treatment Failure" rate of 16.9 per cent.

These were all private patients. For economic reasons, as improvement began, the time interval between office visits was increased to weekly, every two weeks, and then monthly. It is possible that had Kutapressin been given more frequently a considerably greater number of patients would have responded to treatment.

It is interesting to note that the total amount of Kutapressin given in all three groups was approximately the same. Improvement was usually noticeable between the fifth and tenth injection. From this study one can say that if there has been no improvement after fifteen injections, there is not likely to be any even if the injections are continued.

Herpes Zoster. When one begins to study the value of any drug it is fairly easy to form the habit of trying to use it for most, if not every disease. It was probably from such an approach that herpes zoster fell into this evaluation. No report of its use in herpes zoster has been found in the literature, although undoubtedly it has been used.

A total of 24 patients were treated and the series is small. Injections were given daily or on alternate days with the number of injections averaging four or less. It was felt that the severity of discomfort was lessened and the duration of discomfort shortened. Vesicles seemed to dry up more quickly. No other treatment was used in this series.

In such a self-limited condition, a good response in 90 per cent of the patients would be expected. Eighty-three per cent were brought under control with an average of 3.5 injections (Table 2).

Poison Ivy. Kozelka and Marshall[18] reported: "Twenty-eight patients with poison ivy were treated with daily injections of Kutapressin of 2 cc. and every patient responded to this treatment, usually sufficiently improved by the third day to warrant discharge from further care." From their results they concluded that this drug is specific for the relief of symptoms and healing of lesions of poison ivy. White[19] has stated: "It is amazing the number of cases I have had which did not respond to the steroids but did respond to Kutapressin."

In this study there were 50 patients. Kutapressin was given daily or every other day. Adjunctive treatment consisted either of boric acid compresses or starch baths. Discomfort and vesiculation was promptly relieved. When the stage of dryness of the skin developed Kutapressin ointment was occasionally prescribed.

In view of a failure rate of only 2 per cent it is felt that this treatment regimen is at least as specific as any other ever used. It has one other practical advantage,—the physician is given the opportunity of satisfying the public demand for "shots" with an effective and harmless drug (Table 3).

TABLE 2

HERPES ZOSTER (24 Cases)

	Cases		Treatment	
	Number	Per Cent	Average Number of Injections	Average Total Dose
Under Control	20	83.33	3.5	7.0 cc.
Improved	3	12.5	4.0	8.0 cc.
Treatment Failure	1	4.16	3.0	6.0 cc.

TABLE 3

POISON IVY (50 Cases)

	Cases		Treatment	
	Number	Per Cent	Average Number of Injections	Average Total Dose
Under Control	43	86.0	3.5	7.0 cc.
Improved	6	12.0	3.0	6.0 cc.
Treatment Failure	1	2.0	3.0	6.0 cc.

TABLE 4

PSORIASIS (33 Cases)

	Cases		Treatment	
	Number	Per Cent	Average Number of Injections	Average Total Dose
Under Control	6	18.18	36	72.0 cc.
Improved	26	78.78	36	72.0 cc.
Treatment Failure	1	3.03	36	72.0 cc.

Psoriasis. Kutapressin was used experimentally in 36 patients with long-standing psoriasis. Observations were made over a three year period. The study was begun on a definitely controlled basis. There was no doubt of the diagnosis in any case. All other treatment was discontinued. The patients were asked to volunteer for a research study. They were told that there would be no charge for the drug or its administration. A treatment schedule of three injections per week for 3 months was set up. It was understood that if for any reason there was any definite variation of this they would be dropped from the study. Some of the patients were taught to administer the drug themselves. They were impressed and became very enthusiastic. The patients were encouraged to feel that they were making a contribution to medical science. In this way the patients were kept under treatment and observation.

The total prescribed number of 36 injections of 2 cc. was completed by 33 patients. Failure to obtain any response was encountered in only one case. Improvement was manifest by a decrease in itching and cessation of scaling. Spreading was stopped and no new lesions developed. These changes usually appeared about the end of the first month of treatment. The six cases listed "Under Control" relapsed when the drug was discontinued, as had all of the others who were seen later (Table 4).

Kutapressin relieves the symptoms of psoriasis. It is not a cure for psoriasis, but its effect is more than just a psychic effect of new therapy. To be effective it must be used continuously.

TABLE 5

PITYRIASIS ROSEA (19 Cases)

	Cases		Treatment	
	Number	Per Cent	Average Number of Injections	Average Total Dose
Under Control	15	78.94	5.9	11.8 cc.
Improved	2	10.52	8.5	17.0 cc.
Treatment Failure	2	10.52	5.0	10.0 cc.

Pityriasis Rosea. Seventy-nine per cent of 19 patients with pityriasis rosea were brought "Under Control" with Kutapressin (Table 5). However because the disease is self-limited, one would hope for a somewhat better response than this.

TABLE 6

SEBORRHEIC DERMATITIS (183 Cases)

	Cases		Treatment	
	Number	Per Cent	Average Number of Injections	Average Total Dose
Under Control	126	68.85	9.1	18.2 cc.
Improved	49	26.88	11.8	23.6 cc.
Treatment Failure	8	4.37	9.6	19.2 cc.

Seborrheic Dermatitis. Statements have been made to the effect that Kutapressin reduces oiliness of the skin. Since a large number of patients were available (many seen previously for acne) this study was begun to check the validity of these statements. In addition to Kutapressin they were treated with Selsun, topical steroids and other recognized methods (Table 6).

While patients responded to this treatment, in view of the present ease of controlling seborrhea, the therapeutic advantages obtained from a regimen including an injection twice weekly for four weeks or more does not outweigh the inconveniences.

Urticaria. White[20] stated that he has successfully used Kutapressin in the treatment of giant urticaria. His series at that time included 18 patients. Seventeen of them had received the steroids with no benefit but were benefited by Kutapressin. One patient did not respond to Kutapressin but the steroids did help him considerably.

Our group of 64 cases consisted primarily of urticarial reactions resulting from penicillin and other antibiotics. Injections of 2 cc. were given daily at first, then less frequently.

TABLE 7

URTICARIA (DRUG) (64 CASES)

	Cases		Treatment	
	Number	Per Cent	Average Number of Injections	Average Total Dose
Under Control	48	75.0	6.0	12.0 cc.
Improved	9	14.06	6.0	12.0 cc.
Treatment Failure	7	10.93	9.9	19.8 cc.

TABLE 8

ECZEMA OF THE HANDS (83 CASES)

	Cases		Treatment	
	Number	Per Cent	Average Number of Injections	Average Total Dose
Under Control	24	28.91	11.2	22.4 cc.
Improved	30	36.13	11.6	23.2 cc.
Treatment Failure	29	34.94	11.5	23.0 cc.

The purpose of this investigation was to see whether Kutapressin would be of any value in the control of urticaria of a known etiology when the use of the steroids was not desirable. Ninety per cent of these cases had definite improvement both subjectively and objectively. There was, however, a failure rate of 11 per cent in spite of the fact that the injections were continued (Table 7).

No attempt has been made to see if Kutapressin given in conjunction with the steroids and antihistamines might give more improvement and shorten the duration.

Eczema of the Hands. Kutapressin was used as an adjunct to other forms of therapy in the treatment of 83 patients with eczema of the hands. Since less than 30 per cent of the patients were controlled and approximately another 30 per cent failed to respond satisfactorily, it seems that the drug offers little advantage in treating the difficult problem of eczema of the hands (Table 8).

Diseases Not Responding to Kutapressin. Out of curiosity Kutapressin was tried empirically in several other dermatologic disorders, with no response. The following conditions were treated and resulted in failure:

Mycosis fungoides—1
Stevens-Johnson syndrome—5
Hyperirdosis (palm and soles)—3
Haley and Haley—2
Alopecia areata—4
Lichen planus—5
Neurodermatitis and pruritus ani—16
Pyodermia—13
Fungal infection feet—14 (?)
Tinea versicolor—14 (?)

Comments

1. We need to know more in regard to what this drug is, its mode of action and its optimal dose.
2. It cannot be said that Kutapressin has cured any disease studied in this series.
3. The most dramatic results have been in poison ivy and herpes zoster. These conditions are self-limited.
4. It is felt that Kutapressin is a valuable adjunct to the therapy of acne vulgaris.
5. It does something to psoriasis but has not cured any case and has not prevented relapses.
6. In drug eruptions results are not as dramatic as with the steroids although Kutapressin seems to give a similar but more prolonged response.

Summary

The findings of this study are summarized in table 9. Kutapressin is a valuable adjunct in the treatment of acne vulgaris, herpes zoster, and contact dermatitis from poison ivy.

In acne vulgaris sixteen 2 cc. injections given twice weekly are required to obtain maximum effect. The response of the lesions

TABLE 9

SUMMARY (711 Cases)

			Treatment Success		Treatment Failure	
	Diagnosis	Number	Per Cent Improved	Number of Treatments (Aver.)	Per Cent Failure	Treatments (Aver.)
I	Acne	178	83.14	Aver.—15.5	16.86	14.8
II	Herpes zoster	24	95.83	Aver.— 3.75	4.16	3.0
III	Poison ivy	50	98.0	Aver.— 3.25	2.0	3.0
IV	Psoriasis	33	96.96	No.—36	3.03	No.—36
V	Pityriasis rosea	19	98.46	Aver.— 7.2	10.52	5.0
VI	Seborrhea	183	95.73	Aver.—10.45	4.37	9.6
VII	(Drug)	64	89.06	Aver.— 6.0	10.93	9.9
VIII	Eczema hands	83	65.04	Aver.—11.4	34.94	11.5
IX	Miscellaneous	77	ALL FAILURES			
	Total	711				

in 83 per cent of this series of patients was considered a treatment success.

Herpes zoster responded to an average of four 2 cc. injections, first daily, then less frequently.

Three to four 2 cc. injections relieved discomfort and decreased vesiculation in contact dermatitis due to poison ivy.

Patients with psoriasis obtained symptomatic relief,—freedom from itching, scaling, and spreading as long as they took the medication. When it was discontinued the condition relapsed. It was felt that the effects of Kutapressin were greater than could be expected from the psychic effect of new therapy.

The response in pityriasis rosea was good. However, no definitive statement as to the effectiveness of the medication should be made because of the nature of the disease and the small number of patients treated.

While there was a definite response to the therapeutic regimen for seborrheic dermatitis, the advantages of including injections in the regimen are outweighed by the inconvenience.

Kutapressin was used successfully in treating 89 per cent of 64 patients experiencing urticarial reactions to antibiotics. On the average six injections were required.

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Discussion (Abstract)

Dr. Joseph Farrington, Jacksonville, Fla. Good research, like a baby, is oftentimes easy to conceive but hard to deliver. Dr. Barksdale is to be commended on his well-documented studies showing, empirically at least, that here is a therapeutic agent effective in a number of dissimilar and apparently unrelated skin conditions. One preparation effective in such a wide range of conditions may have, however, a common therapeutic denominator. This has perhaps been demonstrated by Marshall who reported a drop of 0.3 of a degree in the facial skin temperature in a normal subject after the administration of 1 cc. of Kutapressin, a measurable pharmacologic effect by use of a thermocouple. It was concluded that a vasoconstriction of the skin vessels ensued for the complexion of the subject blanched. Favorable reports in such conditions as Raynaud's phenomenon and Buerger's disease must be viewed with some circumspection, when one realizes he is administering an agent capable of producing further vasoconstriction, unless one postulates some other pharmacologic actions as yet undetermined.

Through the generosity of the Kremers-Urban Company, we have been supplied with considerable amounts of Kutapressin and have, over a period of several years, conducted studies paralleling those of Dr. Barksdale. Our studies have been limited to only three categories of diseases, namely, acne, keloids and allergic reactions.

I believe all investigators are in agreement that Kutapressin is a valuable adjunct in the treatment of acne, as has been substantiated by such able investigators as Burks, Nierman, Pensky and Goldberg.

Our own experiences would indicate that Kutapressin is much more effective in keloids than Dr. Barksdale has stated. In a series of 25 cases in private practice and the clinic, it was felt that at least 10 showed a good response. I am frank to admit that some of these may have been hypertrophic scars rather than true keloids. I recall vividly the first patient I treated. He was a soldier recently returned from Korea with a severe acne keloidalis. His treatment consisted of exposure to ultra-violet light and the intramuscular injection of 2 cc. of Kutapressin every 5 days. At the end of 6 weeks, I would estimate his improvement at about 75 per cent. It is my clinical impression that the keloids in the white race respond more readily to Kutapressin than those in the colored races.

I am not nearly so enthusiastic as Dr. White in his glowing reports about the efficacy of Kutapressin in urticaria and drug eruptions. I will agree with Dr. Barksdale in his comment that in drug eruptions, results are not as dramatic as with steroids but it seems to give a similar but more prolonged response. As a matter of practical management, we have found that treatment for the immediate control may be obtained with corticosteroids and treatment continued with Kutapressin. Dr. Barksdale alluded to it briefly in his paper, but I would like to ask him how effective he

has found Kutapressin used topically, for (as he has pointed out) with Kutapressin, one is given the opportunity of satisfying the public demand for "shots." There is equally as large a number of patients just as adamant about not getting an injection. I know of no reports of allergic reaction to Kutapressin. It is still relatively expensive and is not a panacea but, with such able investigators as Dr. Barksdale, I am sure it will soon settle down into its proper sphere of usefulness.

Dr. James Q. Gant, Jr., Washington, D. C. Dr. Barksdale is to be congratulated on his study of Kutapressin in such a large number of patients having a variety of dermatological disorders. I have used Kutapressin in psoriasis, acne vulgaris, and rosacea over a period of 4 years.

Psoriasis. This is one of the most difficult diseases to evaluate as regards therapy. It is prone to spontaneous remissions and relapses, and the patients are susceptible to the psychic effect of new therapy. I have used Kutapressin in the treatment of 76 such patients, observing them over a period of 18 months. The lesions of 14 patients cleared up completely and have remained so to date under continuous treatment. Another 54 patients responded very well but did not clear up completely. The remaining lesions generally involved the knees and elbows. Still another 5 patients responded fairly well; 3 patients failed to respond at all. Some patients relapsed when treatment was discontinued but responded again when treatment was resumed. With a regimen of 2 cc. intramuscularly, three times weekly, one or two months of treatment was necessary before effects of treatment were evident. I think Kutapressin has a beneficial influence on psoriasis above and beyond the capricious nature of the disease.

Acne Vulgaris. Forty patients in the age range of 18 to 30 were treated during a period of 12 to 18 months. Patients with severe pustular acne did better than the mild indolent cases and about two-thirds of those with the former responded satisfactorily. The dosage schedule was 2 cc. twice weekly.

Rosacea. Eighteen patients with extensive rosacea were treated over a period of 16 months, being given 2 cc. injections twice weekly. Good response was obtained in 11 of 18 patients; the others showed some improvement. The permanence of treatment response is complicated by the effect of emotional stress of the patient; the physician must use every means available to give the patient a new outlook toward his life's problems.

Kutapressin is well tolerated at the site of injection. I have not seen any general or systemic reactions to it.

Dr. William Poole, Birmingham, Ala. Kutapressin has interested me for the past five years in its effect on herpes zoster, having used it in 100 cases, alternating it with either injections of 100 mg. of vitamin B_1 and 1,000 mcg. of B_{12}. The effects was compared with the purpose of preventing post-herpetic neuralgia. Our results were difficult to evaluate since many cases are mild and there is spontaneous recovery without neuralgia.

None of the cases treated with Kutapressin developed post-herpetic neuralgia. On the average the pain improved progressively to be gone by the tenth day,—practically always within two weeks. In 5 cases injection of 2 cc. twice weekly for two months were required before the pain cleared entirely. This compared almost exactly with those who received injections of either vitamins B_1 or B_{12}.

It is theorized that since Kutapressin, in experimental work, reduces intracellular edema, the lessening of swelling within the ganglion is responsible for the cessation of pain.

Five cases of neuralgia which had existed two months without treatment other than local applications, responded in 6 to 12 weeks with Kutapressin twice weekly. Cases of neuralgia lasting for 6 months after herpes zoster have responded only slightly to any treatment we have been able to offer.

Doctors in Public Life

William Shippen of Pennsylvania, was a member of the Continental Congress and a dedicated physician all his life, one of the founders of the College of Philadelphia (later University of Pennsylvania) and of the College of New Jersey (later Princeton).—(From the A.M.A. Special Report 84-30, 1956.)

David Ramsey of South Carolina, where he moved from Philadelphia, was an Army surgeon during the Revolution. Captured at the fall of Charleston, he was imprisoned by British for 11 months. Later, a member of Continental Congress and at one time its President pro tempore, he instituted the first election contest ever filed before Congress.—(From the A.M.A. Special Report 84-30, 1956.)

Incidence of Allergy in General Practice*

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The author has used an approach different from others to estimate the incidence of allergy in a population group.

ANY PHYSICIAN whose task it is to administer to the medical needs of a community must sooner or later be impressed with the frequency of allergic manifestations. Although it is often stated that approximately 10 per cent of the people are allergic, the exact incidence of allergy in the total population has never been determined. To estimate this incidence, a number of surveys have been done at different times and places, using different methods of obtaining statistical information. As a result, the incidence of allergy has been reported to vary from 7 to 60 per cent.[1-7] Since none of these surveys has made use of the office records of a general practitioner, it seemed worthwhile to determine the frequency and type of the various allergic conditions which actually bring the patient to the doctor's office.

Source of Data

The statistics for this report were taken from the case histories which accumulated during the 17 month period from June 1949 through October 1950, while in general practice in Eudora, Kansas, having a population of approximately 1,000. This survey was contemplated for about the last 6 of the 17 months, and attempts were made to include in the patient's office records as many notes as possible concerning the family and personal history of allergy and also as many of the specific sensitivities as were known or strongly suspected by the patient. No skin tests were done.

Criteria

A brief discussion of certain general considerations may help to point out some of the difficulties encountered in establishing criteria for the diagnosis of the allergic state. In an endeavor to avoid confusion, the word "hypersensitivity" will not be used interchangeably with "allergy" and "atopy." Hypersensitivity is the more inclusive term, and where it is used it will mean increased sensitivity regardless of the mechanism involved. Allergy will denote a type of hypersensitivity in which skin sensitizing antibodies are presumed to react with specific antigen. In this paper, allergy and atopy will be used interchangeably which seems to be the common usage, although this practice is incorrect according to the historical definition of the words.[8,9]

If one attempts to include all types of diseases which might be produced by a hypersensitive reaction, controversial issues arise over whether certain conditions should be considered allergic. For example, nearly 85 per cent of all adults have positive skin reactions to tuberculin, demonstrating hypersensitivity to this antigen. Also, 75 per cent of individuals are thought to be sensitized to poison ivy after the first contact. If contact dermatitis and positive tuberculin reactions are considered "allergic," as indeed they might be according to some definitions, practically everyone is allergic. However, bronchial asthma, seasonal hay fever, chronic nasal allergy, gastrointestinal allergy and certain forms of urticaria, eczema and migraine have long been regarded to be typical manifestations of the inherited type of allergy or atopy. This is not an arbitrary classification but is a naturally occurring arrangement, since two or more of these conditions in different combinations often coexist in the same patient. For the purpose of this survey, only patients with the foregoing conditions were included. Even then there were reasons to doubt whether certain patients, especially some having urticaria and headache should be classified as being allergic. The dis-

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tinction is not always important insofar as symptomatic treatment is concerned. It is important here to make the differentiation for statistical purposes.

In order to fulfill the requirements of atopy, the following conditions are necessary:[4,10,11] (1) positive family history of allergy; (2) positive immediate whealing skin tests; (3) circulating skin sensitizing antibodies capable of producing positive passive transfer tests; (4) blood eosinophilia, not attributable to other disease; (5) characteristic symptoms not adequately explained on any other medical basis; (6) the presence of, or a personal history of another of the accepted diseases of allergy; and (7) characteristic response to anti-allergic drugs.

As stated, no skin tests were done on these patients. Therefore, the following rules were adopted: All patients with seasonal hay fever or seasonal asthma were included. Patients with perennial nasal allergy and asthma were included, if the family background was positive for allergy, or if a history of allergy to a substance could be obtained. Those patients whose presenting complaint was either eczema, headache, urticaria or gastrointestinal disturbance were not considered allergic unless there was evidence of known allergy to a specific substance, or unless there was also a personal history of a more common manifestation of allergy, such as hay fever or asthma. By following these rules, it was felt that it would be possible to more nearly approach an accurate incidence of allergy in general practice.

Using these criteria, 113 of the 1,170 patients seen, or 9.65 per cent were found to be allergic. The majority of these patients had more than one allergic disorder, making a total of 185 manifestations which were recognized in 113 allergic patients (Tables 1 and 2).

TABLE 1

PRESENTING COMPLAINTS OF 113 ALLERGIC PATIENTS

	Number Allergic	*Per Cent of Total*
Chronic nasal allergy 11 (including complications) 35	46	3.93
Asthma	35	2.99
Hay fever	11	0.94
Gastrointestinal allergy	8	0.68
Other than allergy	5	0.43
Urticaria	4	0.34
Eczema	3	0.26
Migraine	1	0.08
	113	9.65

TABLE 2

ALLERGIC MANIFESTATIONS RECOGNIZED IN 113 ALLERGIC PATIENTS

	Manifestations
Chronic nasal allergy	78
Asthma	52
Hay fever	31
Gastrointestinal allergy	11
Urticaria	8
Eczema	3
Migraine	1
Physical allergy	1
	185

Discussion

Chronic nasal allergy was the most frequent manifestation observed. The nasal symptoms were not particularly disturbing to most of the patients except during exacerbations, which were often accompanied by infection of either the nasal passages, the paranasal sinuses, or less frequently the middle ear. In these instances the acute infectious process was the presenting complaint and it usually overshadowed the less annoying allergic symptoms. It was observed that the nasal infections had a tendency to recur more often if the nasal allergy was not controlled. Some of the common statements made by these patients were, "I have one cold right after another," "I've had sinus trouble for years," or "I always have a cold, but never have a fever." The recognition of the fact that from the patient's point of view allergic nasal symptoms may often resemble infection is important, and this was always carefully considered before arriving at the diagnosis of nasal allergy.

Asthma ranked second from the standpoint of the number of patients observed. However, more time was devoted to caring for this group of allergic patients than to any of the others. There are, of course, many varieties of asthma which can occur in atopic individuals, such as: acute, chronic, seasonal, perennial, infectious, extrinsic, or intrinsic. No distinction between types is made in this survey. However, several patients who had attacks of wheezing were not included because other typical findings of allergy could not be confirmed.

Seasonal nasal allergy or hay fever, although

fairly common among allergic individuals, was found to be surprisingly infrequent as a presenting symptom when compared with the incidence reported in earlier surveys, despite the fact that the community is located in a heavy pollen producing area.

Gastrointestinal symptoms due to allergy were observed as a presenting complaint in 8 of this group of patients. Three of the 8 were adults and 5 were children. All were allergic to various foods which were known to reproduce the gastrointestinal symptoms and all of them had other allergic disorders.

Urticaria is a manifestation of a hypersensitive reaction, but certainly not all instances represent spontaneous or hereditary human allergy. For example, sensitivity to penicillin or horse serum can be acquired by anyone. However, in the 8 patients whose urticaria was classified as atopic, it was the chief complaint in 4 and in the remainder an associated manifestation of other allergic conditions. These 8 patients are only a portion of the total number of patients seen with urticaria, the remainder having no evidence of inherited allergy.

Although eczema, migraine and physical allergy are not common allergic manifestations, there was a definite incidence of each condition. Two of the eczema patients were children and one was an adult. All 3 had typical flexural distribution of the skin lesions, which is characteristic of atopic eczema and all of them had other allergic manifestations. The migraine patient was a girl, age 12 years, who had suffered with recurrent unilateral headaches and chronic nasal allergy for 5 years. Her father, brother and sister were also allergic. The patient with physical allergy had seasonal hay fever in the fall and was incidently disturbed by wheals which occurred on exposure to cold.

Another group of patients included in this survey were those who sought treatment for conditions other than allergy, but from whom a history of current allergic manifestations was readily obtained. If one patient out of ten is potentially allergic, it is not amiss to spend a few minutes questioning every new patient concerning his allergic background.

Comparison Not Possible

Direct comparisons of percentages between any surveys of allergy, including this one, is not possible because no two of the investigations were conducted alike. The difference in the results will be better understood by reviewing the methods used in gathering the statistical information, as well as the criteria used for the diagnosis of the allergic state, all of which are summarized in table 3.

It seems apparent that questioning persons

TABLE 3

Cooke and Vander Veer[1]	Method:	68 individuals selected at random were questioned regarding themselves and their parents,—a total of 204 individuals.
1916		
7%	Criteria:	Clinical history of sensitization.
Spain and Cooke[6]	Method:	Determination of incidence in 506 individuals by lay investigators.
1924		
7%	Criteria:	Clinical history of hay fever and asthma.
Jimenez[2]	Method:	Data obtained from questionnaires filled out by 7,000 enrolling university students.
1934		
11.9%	Criteria:	Those who checked eczema, rose fever, hay fever, or asthma (11.9%) plus those who checked urticaria, gastrointestinal upsets, food idiosyncracy, frequent "colds," headache, etc., with positive family history of sensitization. (22.27%)
22.27%		
34.17%		
Vaughan[7]	Method:	Trained social investigator house to house canvas,—508 persons living in vicinity of Clover, Virginia.
1934		
10% major	Criteria:	Not given—presumed to be asthma, hay fever, eczema, migraine, gastrointestinal allergy and urticaria requiring professional attention.
50% minor		
60%		
Pipes[3]	Method:	Amnesic survey conducted with assistance of 3 school teachers, 2 of whom were allergic. There were 700 persons questioned.
1937		
15.6%	Criteria:	Hay fever, asthma, migraine, urticaria, eczema, angiodema, and colitis of severity necessitating professional attention.
Rowe[4]	Method:	Questionnaire answered by 2,000 university students.
1937	Criteria:	Personal history of asthma, hay fever, urticaria, eczema, or headache.
33%		
Service[5]	Method:	House to house canvas by two men from Dept. of Biology at Colorado College. All questionable cases studied by Dr. Service.
1938		
22.6%	Criteria:	1,000 families consisting of 3,141 persons were interviewed. Hay fever, asthma, eczema, migraine, urticaria, and gastrointestinal allergy severe enough to require medical relief.

concerning all of their life would yield a higher incidence of allergic manifestations than would be obtained by following the same group of persons for only 17 months and recording how many of them consulted a doctor for their allergic disorders during that limited period of time. In other words, this survey would not be expected to identify all of the patients of the group considered who had ever experienced an allergic reaction in their lifetime.

Summary

This survey was an attempt to identify and classify the percentage of allergic patients encountered in general practice. During a 17 month period a total of 1,170 different patients visited the office for medical attention. Of this number, 113 or 9.65 per cent were diagnosed as currently suffering from some form of allergic disorder according to the criteria outlined.

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Doctors Who Signed the Declaration of Independence

Matthew Thornton, a contemporary of Dr. Bartlett and the third signer of the Declaration of Independence, was a colonel in the New Hampshire troops almost 30 years before the Revolutionary War. Massive physically as well as mentally, he is said to have had "black and penetrating eyes and an invincibly grave expression." After one session of the Continental Congress, he was appointed to his state's supreme court and thereafter did not practice medicine. One example of his mental capacity: when past 80 years of age he wrote a metaphysical treatise.

Lyman Hall, another signer of the Declaration of Independence, was born in Connecticut, graduated from Yale, then migrated to St. John's Parish on the Georgia coast, where he gathered around him a colony of intellectuals and independents. When he arrived at the Continental Congress in 1775, John Adams described him as "intelligent and spirited . . . made a powerful addition to our phalanx." Like Dr. Bartlett and most of the others, he suffered for his views. His home was burned by the British in 1778. Later, as governor of Georgia, he helped to found the University of Georgia. Throughout his career he practiced medicine while also prospering as a rice planter.

Benjamin Rush of Pennsylvania, another practicing physician who signed the Declaration of Independence, was easily the most famous American physician and medical teacher of his generation. Dr. Rush was a rugged character, brash and bold in debate and in conduct. His correspondence was so indiscreet—he feuded violently with Washington, among others—that his family kept his private papers secret until recent years. He was a confidant of all the important men of his age in political life. It was to him that Jefferson wrote the famous line: "I have sworn upon the altar of God eternal hostility against every form of tyranny over the mind of man."—(From the A.M.A. Special Report 84-30, 1956.)

CASE REPORT

Convulsions Following Withdrawal from Meprobamate: Report of Two Cases

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WITHIN THE LAST FEW YEARS there has been a marked increase in the use of chemotherapeutic agents in the treatment of psychiatric disorders. This has been paralleled by the growing use of "tranquilizing" drugs by general practitioners and nonpsychiatric specialists. One of the recent additions to the list of these medications is meprobamate (Miltown, Equanil). This drug may be even more widely used in office practice than have been chlorpromazine and the rauwolfia alkaloids. In spite of the great demand by the general public for meprobamate, and its general acceptance and employment by the medical profession, there have been surprisingly few carefully controlled clinical studies of its effects. None of the early reports described addictive properties. Friedman and Marmelzat[1] reported a number of adverse reactions to meprobamate, particularly dermatoses, but did not describe withdrawal symptoms.

Lemere[2] has recently called attention to some of the habit forming properties of meprobamate. He describes an increase in tension above the premedication level when the drug is stopped, and cites several cases in which patients voluntarily stopped the drug for fear of becoming "addicted" or too dependent upon it. He mentions one patient who had a convulsive seizure ten hours after discontinuing the drug. This patient had been receiving 6.4 Gm. of meprobamate daily for the previous month. The patient had no history of previous convulsions, and no subsequent seizures up to the time of the report.

At the Oklahoma Medical Center, two patients have been studied who experienced a marked symptomatic reaction, culminating in grand mal seizures, following withdrawal of meprobamate.

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Case Reports

Case 1. A 68 year old housewife was admitted to the Psychiatric Service of the University of Oklahoma Hospitals in December, 1955, with an eight year history of gradually progressive symptoms including bodily overconcern, tension, brooding, insomnia, and dependence on barbiturates. She became demanding, irritable, critical of her husband, and disinterested in her home, friends, social and community activities. She was preoccupied with her diet and bowel functions. Restlessness was extreme, and she was unable to sit still for more than a few minutes.

On admission to the hospital, the patient was slightly groggy from barbiturates (phenobarbital), but was a well-groomed and handsome woman. She spoke volubly and rapidly, but was evasive and irritable when questioned. She stated, "I'm an old woman; just give me sedatives and let me sleep." She described her situation as hopeless, but did not appear markedly depressed or retarded. She was preoccupied with numerous somatic complaints and continually asked for sedatives. She was well oriented and had no memory defects. There was no history of seizures.

Physical examination was negative. An electroencephalogram was unsatisfactory because of her restless movements.

The patient adjusted poorly to the hospital. She was self-centered, restless, critical of others, hostile and aloof. She was unable to sit quietly for more than a minute or two during interviews. Her sleep was broken, and averaged three to four hours nightly with the use of chloral hydrate. Barbiturates were discontinued and she was given chlorpromazine as an adjunct to psychotherapy, with very little effect on her subjective state or behavior short of stupefying doses. On July 24, 1956, chlorpromazine was discontinued and the patient was given meprobamate, 2.4 Gm. daily, with a slight sedative effect being noted. This dosage was gradually increased to 5.6 Gm. daily, as the patient complained bitterly that it was not helping her enough, and constantly asked to be put back on chlorpromazine. Because she gradually became more restless and depressed, meprobamate was

discontinued on October 26, 1956. There was an immediate increase in tension and restlessness. She complained of palpitations, refused to go to bed at night and continually paced the corridor, although small doses of chlorpromazine (25 mg. 4 times daily) were given.

She was agitated, markedly irritable, complained of feeling hot and of extreme malaise. For the first time nausea and vomiting appeared. The patient's facial expression was dazed and frozen, and there was transient disorientation and memory difficulty. On October 28, 1956, fifty-two hours after meprobamate was discontinued, the patient had a grand mal seizure while looking at a television screen. Postictally she showed transient weakness of the left leg, was confused and disoriented. Chlorpromazine was discontinued. Four hours later she had a second grand mal seizure while in bed, and a third seizure 4 hours after that. Small doses of phenobarbital were administered. The patient recovered completely from this episode without sequelae. The electroencephalogram, 24 hours after the seizures, was mildly abnormal with some asymmetrical 3 to 5 per second slowing and focal simple spikes. The tracing reverted to normal within three weeks. There were no further seizures, and the patient has since been discharged from the hospital, much improved, apparently on the basis of her continuing psychotherapeutic relationship with the resident in charge of her case.

Case 2. A 21 year old housewife sought psychiatric treatment in the spring of 1955, because of an emotional disturbance associated with four stormy years of marriage. Meprobamate was started in October, 1955, and at first she received marked relief in the form of relaxation. Her symptoms of anxiety, tension, irritability, depression, and brooding were much improved by the drug. With unremitting marital strife, however, it was necessary for her to continue with the medication. Its effects became less and less satisfactory despite a steady increase of dosage. Finally, she decided it was no longer helping her and tried to stop taking it. Dosage at that time was approximately 2.4 Gm. daily. She experienced withdrawal symptoms of marked tension, fearfulness, weakness, tremulousness, insomnia, and malaise, and had to resume the medication within a day. Because of panic over the idea of being addicted she went to another psychiatrist, requesting hospitalization for withdrawal symptoms. She was admitted to the private service of the University of Oklahoma Hospital on November 20, 1956.

Past history was not greatly contributory except for the emotional disturbance previously noted. There was no history of a convulsive disorder. Physical examination was negative.

No meprobamate nor other sedation was given following admission to the hospital. The withdrawal syndrome described above reappeared. Approximately 30 hours after her last dose, without warning, the patient had a grand mal seizure striking the back of her head severely in the fall. She was subsequently stuporous for about 12 hours and had some bleeding from the right ear. The clinical picture was that of a basilar skull fracture with concussion, but radiologic studies did not reveal the fracture.

On examination, 72 hours later, there was a slight impairment of hearing in the right ear. The patient was alert, oriented in all spheres, cooperative and intelligent. She showed some anxiety, tension, resentment, and depression. She was markedly self-centered, narcissistic, and immature. There were no delusions, hallucinations, or distortions of reality. The electroencephalogram two weeks after the seizure was normal, and there have been no subsequent seizures.

Comment

Convulsions are not uncommon following withdrawal from certain drugs, particularly barbiturates and alcohol. It took many years for American physicians generally to become aware of the addictive qualities and the alarming syndrome associated with the abrupt withdrawal of barbiturates.[3]

The cases here reported reinforce the growing awareness of similar (albeit less common) hazards associated with the use of meprobamate. The syndrome described in both cases is in many ways like the reaction associated with withdrawal following prolonged use of barbiturates. Presumably the mechanism is similar in the production of convulsions.

As with barbiturates, meprobamate should be withdrawn cautiously over a period of several days. It may be tempting, when prolonged and increasing doses of meprobamate fail to produce or maintain the desired effect, to discontinue the drug and substitute the more "potent" chlorpromazine. In view of the cortical excitatory effects of chlorpromazine this would seem to be unwise unless a suitable period of time is allowed to intervene.

Summary

Convulsions and other withdrawal symptoms are reported in two patients following the discontinuance of meprobamate. During the period of medication both patients showed a developing tolerance, requiring larger and larger doses to produce the desired effect. One patient described a craving for, and sense of habituation to the drug and a fear of addiction. It appears that meprobamate may cause habituation and addiction in certain patients, and that it is in some ways similar to barbiturates in this regard.

When patients have been taking large amounts of meprobamate for long periods, or have developed craving and demonstrated tolerance, the drug should be discontinued

gradually over a period of days. Withdrawal symptoms should be treated like barbiturate withdrawal symptoms, and phenothiazine derivatives like promazine and chlorpromazine should not be administered during the withdrawal period. Meprobamate should be used with caution and under the close supervision of a physician, particularly in patients with a history of dependence on drugs or alcohol.

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EDITORIALS

TESTING FOR SENSITIVITY BEFORE GIVING PENICILLIN

In 1955, attention was directed on these pages to the hazards accompanying sensitivity to penicillin. The occasion for the first editorial comment[1] was the publication of a couple of papers dealing with an increasing number of deaths due to anaphylactic shock following the injection of penicillin, and with the incidence of a positive history of cutaneous reactions due to penicillin given some time previously. The second editorial[2] was stimulated by the use of penicillin as a preservative in polio vaccine, and the, at least theoretical, possibility of sensitizing a person to these antibiotics by successive doses of such vaccine. (Some pharmaceutical houses were changing to another antibiotic as a preservative at that time.)

The actual number of deaths due to anaphylactic shock after the injection of penicillin is unknown because few cases are reported. An editorial[3] in the JOURNAL OF THE AMERICAN MEDICAL ASSOCIATION, however, makes an estimate of the number of deaths due to anaphylaxis in this country. On the basis of 7 deaths reported by 1,000 California physicians (0.67 per cent of physicians in the country) in a questionnaire, it is projected that over 1,000 deaths have occurred in the country. The authors of this editorial discussed the use of skin tests before penicillin is given. They suggested first a scratch test with a weak solution of penicillin and, if negative, the doing of an intradermal test. Berger and Eisen[4] reported, after a study of 1,000 cases, that skin tests are not dependable in determining sensitivity to penicillin.

Very recently another study was reported from the Army, using a different technic of testing for sensitivity. Smith[5] used a simplified procedure using a drop of full strength (300,000 units per cc.) procaine penicillin on a scratch 3 to 4 mm. in length made with a hypodermic needle. In addition, he instilled a drop of the same material into the conjunctival sac. After fifteen to twenty minutes these areas were observed for itching, redness, edema and wheal formation at the site of the scratch test, and for itching, watering, redness and edema of the eye.

By using this combined method of testing for the "anaphylactic-sensitive" person, Smith tested 1,365 adults in a period of twenty months. Of these, 567 were subjects selected at random at an Army dispensary from among patients, personnel, associates and visitors. The remainder, 798, were patients who were to receive penicillin. There were 7 who had had anaphylactic reactions after an injection of penicillin at other dispensaries or stations.

Of the 1,365 subjects 64, or 4.7 per cent, gave a history of sensitivity, most of them being of the delayed urticarial type, and fewer of the serum-sickness and the acute anaphylaxis type. Among the 1,365 persons tested only one, who had had penicillin previously without reaction, developed upon testing with the two drops, tachycardia, palpitation, apprehension and dyspnea promptly relieved by epinephrine. By the criterion of a wheal of more than 1 cm. in size at the site of the skin test, and itching, edema and redness at the sites of testing, with watering of the eye, 25 or 1.1 per cent were positive. Some had a positive conjunctival test and negative skin test. One of this latter group desired an injection of penicillin for urethritis; when this was denied he went elsewhere to get the injection and died in anaphylactic shock.

In the group of 798 patients 600,000 units of penicillin were given to 778 after a negative test. Only one had a mild anaphylactic reaction.

Smith points out that these tests are for the purpose of searching out those who might have an acute anaphylactic reaction. They may not predict the delayed urticarial or serum-sickness type of reactions.

It seems timeworthy to comment on this paper since the news-magazine "Time" has

1. Editorial: Inherent Dangers in the Use of Penicillin, South. M. J. 48:664, 1955.
2. Editorial: Penicillin as a Preservative in Polio Vaccine, South. M. J. 48:1256, 1955.
3. Guest Editorial (Feinberg, S. M., and Feinberg, A. R.): Allergy to Penicillin, J.A.M.A. 160:778, 1956.
4. Berger, A. J., and Eisen, Bruno: Feasibility of Skin Testing for Penicillin Sensitivity. A Study of One Thousand Cases, J.A.M.A. 159:191, 1955.
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featured it under the title of *Penicillin Safety* in the October 7, 1957, issue. It seems very likely that some intelligent patients, and especially allergic ones, will ask their physicians to test them, or will wonder why a test is not done.

BCG VACCINATION IN THE UNITED STATES

This country has lagged far behind other countries in vaccination against tuberculosis. This fact has been the cause for comment recently in a Report by the Medical Advisory Committee of Research Foundation.[1] It is said that 150 million persons have been vaccinated among the world's population. Vaccination against tuberculosis is mandatory by law in France, Norway, Denmark, Japan and Brazil. Well-controlled studies in the Scandinavian countries, Great Britain as well as in this country have clearly shown a markedly reduced incidence of tuberculosis among those vaccinated as against tuberculin-negative non-vaccinated controls.

BCG vaccination would seem indicated for those who cannot avoid exposure to infection, those thought to have low resistance, and for those who live in communities having a high mortality from tuberculosis. This attitude has been recommended by the American Trudeau Society and has been recognized by the U. S. Public Health Service, the Council on Drugs of the American Medical Association and the National Tuberculosis Association.

The Report summarizes the objections to the use of BCG in this country by the following posed questions: "(1) Is there a need for BCG vaccination in the United States? (2) Is BCG safe? (3) Is BCG sufficiently well standardized? (4) Is BCG effective in the prevention of tuberculosis in humans? (5) Will the usefulness of the tuberculin test be lost as a diagnostic measure? (6) With chemoprophylaxis, is vaccination necessary?"

The answer to the first question appears in statistics. Though the mortality rates for tuberculosis have dropped in recent years, the number of newly reported cases remains up. The Report says that about 100,000 new cases were reported in this country in 1930 and a like number in 1954. Of the 1,200,000 cases of tuberculosis in the country about 400,000 are active. Also, it is said that 45 per cent of the tuberculous patients are not in hospitals, 87 per cent of these represent advanced cases with 40 per cent having been discharged from hospitals against medical advice and without benefit of drugs or bed rest. The Report further states that there are urban areas in the United States where the incidence of new cases is four times that of the country at large, and that in Chicago there are areas where 11 per cent of the elementary school children and 31 per cent of high school students have positive tuberculin tests. Surely such figures confirm the need for vaccination of certain groups and in certain areas, even though the number of positive reactors is gradually decreasing.

Historically, BCG got off to a bad start in its early days by an increased virulence of the organisms on an occasion. Then there have been untoward local reactions at the site of inoculation. However, by the multiple puncture method used in this country and in the hands of more than 400 users in 47 states complications of vaccination have practically been eliminated. Thus, it appears that BCG vaccination is as safe as other methods of vaccination.

Relative to standardization certain authorities in immunology in the United States say, according to the Report, that as far as biologic standardization goes, always implying some uncertainty, BCG is as well standardized as vaccinia, or even better than the toxoids of diphtheria or tetanus.

Concerning the question of effectiveness of vaccination with BCG the Report refers to 29 controlled studies; admittedly all have been criticized in one way or another. Nevertheless, there have been some impressive Canadian and American studies as to its effectiveness. The Report especially refers to the excellence of the studies under the auspices of the Medical Research Council of Great Britain begun in 1950. This included 56,000 boys and girls between 14½ and 15 years of age in heavily populated areas of three industrial cities. The study showed that there was a reduction of 80 per cent in the incidence of tuberculosis in the half who were vaccinated over that in the control unvaccinated group in the 4 year period of follow-up.

1. Why Have We Not Accepted B.C.G. Vaccination? Report by the Medical Advisory Committee of Research Foundation, J.A.M.A. 164:951, 1957.

In answer to question 5, the Report admits the tuberculin test will lose its value in case finding, but it is felt that this is over-balanced by the decreased incidence of tuberculosis.

Relative to the last question, whether BCG vaccination is necessary when chemoprophylaxis is available, one faces the fact that the use of isoniazid for this purpose presupposes prompt recognition of the "converter"—the formerly tuberculin-negative person having become positive. The matter of continuing a drug for a year in the case of the "converter" in the social class involved in the main, would offer a staggering problem in cooperation, plus the fact that isoniazid does not kill all the organisms. If infection does occur after vaccination, the evidence points to localization of the invading organisms at the site of invasion.

The evidence gathered over the years from all corners of the globe would indicate that the use of BCG vaccination should be more seriously entertained for tuberculin-negative children in urban areas having a high incidence of tuberculosis, for those likely to be exposed in a family which harbors active tuberculosis, and for those young adults who are almost certain of exposure,—medical students, nurses, hospital personnel and the like.

25 YEARS AGO

Therapy in Ovarian Insufficiency and the Menopause*

"There exists at the present time considerable confusion as to the status of ovarian hormone therapy. Rational as ovarian substitution therapy may theoretically appear to be in some conditions, the actual results are rarely striking and often difficult to detect. To some extent this is due to the lack of an objective index of ovarian activity. To this must be added the uncertainty of determining when the case is one of a pure ovarian insufficiency and when it is an anterior pituitary dyscrasia. There is some very convincing evidence as to the efficacy of substitution therapy in experimental ovarian insufficiency in animals. Here, however, one is dealing with pure physiologic insufficiencies and not with the complex clinical syndromes which are encountered in clinical cases. Then, too, the quantities of hormone usually administered to experimental animals are relatively much greater than those ordinarily given to humans.

"There have appeared from time to time convincing reports of the effect of various preparations of the ovarian follicle hormone in conditions of ovarian insufficiency. However, after carefully weighing the evidence . . . the Council of Pharmacy of the American Medical Association decided that, although certain ovarian preparations were shown to be physiologically active, and able to induce oestrus in sprayed animals, their therapeutic activity in the human, and their clinical field of usefulness, had not been sufficiently defined. . . .

" . . . it seemed advisable to study the effect of a known physiologically active preparation, ovarian follicular hormone, in a series of clinical conditions which were commonly regarded as being due to ovarian insufficiency, with a view to substantiating further the work of previous observers, to determine some idea of the necessary dosage in terms of Allen-Doisy units, and to eliminate, as far as possible, all question of any benefits which might occur, being due to coincident nonspecific therapy.

" . . . Only intelligent, cooperative women were chosen. These were seen at regular intervals throughout the period of observation. Two types of cases were selected for treatment: (1) menopause and (2) primary amenorrhea. Of the 10 cases of menopause 2 were artificial and 8 were natural. All were selected because of the severity of symptoms such as hot flushes, pruritus, headache and nervousness. . . .

"The ovarian follicular hormone used was prepared according to Morrell's modification of the Allen-Doisy technique. The unitage of each batch was checked in our own laboratory in sprayed rats, by the vaginal smear method. The hormone was administered by means of vaginal pessaries. . . . The dosage used varied considerably. In general, the principles of beginning with an overdose and diminishing it to the physiologic one was used. This appears to require adjustment in each individual case. During the control periods pessaries of plain gelatin were used and the patients were not informed of the change.

"*Discussion.* Strikingly beneficial results were obtained in 3 of the 8 cases of natural menopause treated with ovarian follicular hormone. In each of these 3 instances the menopause was of less than 1 year's duration. In these cases there was marked relief of symptoms and reestablishment of uterine bleeding. It is fully realized that there is no particular benefit to be gained by reestablishing uterine bleeding after the menopause has set in. In the present experiment it was simply regarded as evidence that the hormone was physiologically active and capable of producing an effect which could not be considered psychic in these cases. . . .

"The 2 cases of artificial menopause both obtained

*Webster, B.: Ovarian Follicle Hormone Therapy in Ovarian Insufficiency and the Menopause, Am. J. M. Sc. 184:822, 1932.

what appeared to be remarkable relief from headaches, hot flushes, and nervousness. In both instances this result did not manifest itself until nearly 1,000 units had been used. The relief continued for approximately 1 week after therapy was stopped during a control period. . . . These 2 cases of artificial menopause could be maintained symptom free on approximately 500 units of the hormone each per month. . . .

" . . . In striking contrast are . . . 2 cases (which) exemplify a group which is usually regarded as being due primarily to anterior pituitary dyscrasia. Their lack of response to the follicle hormone confirms this classification.

"*Conclusion.* A series of 20 cases is presented in which the intravaginal administration of the ovarian follicle hormone has been alternated with control periods. It would appear that the preparation of the hormone used was physiologically active in humans, as evidenced by the induction of uterine bleeding. Further, data are presented which suggest that this hormone of the ovarian follicle is of definite clinical therapeutic value in the treatment of the disagreeable symptoms which may accompany the menopause and of the amenorrhea due to an insufficiency of that hormone. No beneficial results were obtained when the hormone was administered to cases of amenorrhea which showed clinical evidences of an anterior pituitary etiology."

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Spontaneous and Habitual Abortion. By Carl T. Javert, M.D., Professor of Clinical Obstetrics and Gynecology, College of Physicians and Surgeons of Columbia University. 430 pages. New York: The Blakiston Division of McGraw-Hill Book Company, 1957. Price $11.00.

Psychosomatic Medicine. A Clinical Study of Psychophysiologic Reactions. By Edward Weiss, M.D., Professor of Clinical Medicine, Temple University Medical Center, and O. Spurgeon English, M.D., Professor and Head of Department of Psychiatry, Temple University Medical Center. Third edition, 534 pages. Philadelphia: W. B. Saunders Company, 1957.

The Diagnosis and Treatment of Pulmonary Tuberculosis. By Paul DuFault, M.D., Medical Director of the Rutland State Sanatorium, Massachusetts. Second edition, 416 pages with 162 illustrations. Philadelphia: Lea & Febiger, 1957.

Clinical Toxicology. The Clinical Diagnosis and Treatment of Poisoning. By S. Locket, M.B., B.S., M.R.C.P., Senior Physician, Oldchurch Hospital, Romford, Essex. 743 pages with 27 illustrations. St. Louis: The C. V. Mosby Company, 1957. Price $20.00.

The Physiology and Biochemistry of Lactation. By S. J. Folley, Ph.D., Head of Physiology Department, National Institute for Research in Dairying, Shinfield, Reading, Berks. 148 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1956. Price $3.75.

Gynecologic Surgery and Urology. By Thomas L. Ball, M.D., Assistant Professor of Clinical Obstetrics and Gynecology, Cornell University Medical College. 535 pages, illustrated with 161 full-page plates. St. Louis: The C. V. Mosby Company, 1957. Price $20.00.

Role of Hospitals in Programmes of Community Health Protection, First Report of the Expert Committee on Organization of Medical Care. World Health Organization No. 122. 34 pages. New York: Columbia University Press, 1957. Price $0.30.

Expert Committee on Biological Standardization. Tenth Report. World Health Organization No. 127. 35 pages. New York: Columbia University Press, 1957. Price $0.30.

Gastro-Intestinal Obstruction. By Meyer O. Cantor, M.D., Associate Attending Surgeon, Grace Hospital, and Roland P. Reynolds, M.D., Chief of Surgery, Grace Hospital, Detroit. 547 pages. Baltimore: The Williams & Wilkins Company, 1957. Price $18.00.

Prevention of Chronic Illness. Volume 1 of Chronic Illness in the U. S., Commission on Chronic Illness. 323 pages. Cambridge, Mass.: Published for the Commonwealth Fund by Harvard University Press, 1957. Price $6.00.

The Physiology of Induced Hypothermia. Proceedings of a Symposium, October, 1955. Publication No. 451. Edited by Robert D. Dripps, M.D. 440 pages. Washington: The National Academy of Sciences—National Research Council, 1956. Price $3.50.

The Surgical Management of Pulmonary Tuberculosis. Edited by John D. Steele, M.D. 207 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1957. Price $9.50.

Practical Pharmacology. By J. H. Burn, Professor of Pharmacology, University of Oxford. 72 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1957. Price $5.50.

Surgeons All. By Harvey Graham, M.D. 443 pages. New York: Philosophical Library, 1957. Price $10.00.

The Placement of Adoptive Children. By J. Richard Wittenborn, University Professor of Psychology and Education, Rutgers University, New Brunswick, N. J. 184 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1957. Price $4.75.

Therapeutic Exercises For the Treatment of The Neurologically Disabled. By Harold J. Brenner, M.S., Assistant Chief, Corrective Therapy Supervisor of the Neurological Service V. A. Hospital, Sepulveda, Calif. 73 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1957. Price $3.50.

Foot Troubles. By T. T. Stamm, F.R.C.S. 122 pages. New York: Philosophical Library, Inc., 1957. Price $4.75.

Biochemical Disorders in Human Disease. Edited by R. H. S. Thompson, M.A., D.M., Professor of Chemical Pathology, Guy's Hospital Medical School, and E. J. King, Ph.D., D.Sc., F.R.I.C., Professor of Chemical Pathology, Postgraduate Medical School, both of the University of London. 783 pages with 121 illustrations. New York: Academic Press, Inc., 1957. Price $12.60.

An Atlas of The Commoner Skin Diseases. By Henry C. G. Semon, M.A., D.M. Oxon, F.R.C.P. London, Consulting Physician for Diseases of the Skin, and former Lecturer to Postgraduates, Royal Northern Hospital. Fifth edition, 371 pages, illustrated. Baltimore: The Williams and Wilkins Company, 1957. Price $20.00.

Practitioners' Conferences Held at the New York Hospital-Cornell Medical Center. Volume 6. Edited by Claude E. Forkner, M.D., Professor of Clinical Medicine, Cornell University Medical College. 375 pages. New York: Appleton-Century-Crofts, Inc., 1957. Price $6.75.

Physiopathology of the Reticulo-Endothelial System. A Symposium. Edited under direction of B. N. Halpern, Paris. 314 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1957. Price $9.00.

Fluid and Electrolytes in Practice. By Harry Statland, M.D., Associate in Medicine, University of Kansas School of Medicine. Second edition, 217 pages. Philadelphia: J. B. Lippincott Company, 1957.

Management of the Patient with Headache. By Perry S. MacNeal, M.D., Assistant Professor of Clinical Medicine, Bernard J. Alpers, M.D., Professor and Head of the Department of Neurology, and William R. O'Brien, M.D., Instructor in Psychiatry, all of Jefferson Medical College, Philadelphia. 138 pages. Philadelphia: Lea & Febiger, 1957. Price $3.50.

Health Yearbook, 1956. Compiled by Oliver E. Byrd, M.D., Professor of Health Education, Stanford University. 268 pages. Stanford, Calif.: Stanford University Press, 1957. Price $5.00.

The Family in Psychotherapy. By C. F. Midelfort, M.D. 200 pages. New York: The Blakiston Division of McGraw-Hill Book Co., Inc., 1957. Price $6.50.

Clinical Applications of Suggestion and Hypnosis. By William T. Heron, Ph.D., Professor of Psychology, University of Minnesota. Third edition, 159 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1957. Price $3.75.

Abdominal Total Hysterectomy. By Frank Musgrove, M.D. (Lond.), M.R.C.O.G. (Eng.) 32 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1957. Price $2.25.

Suprapubic Closure of Vesicovaginal Fistula. By Vincent J. O'Conor, M.D., Professor and Head of Department of Urology, Northwestern University Medical School. American Lecture Series. 52 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1957. Price $2.50.

SOUTHERN MEDICAL NEWS

ALABAMA

Dr. R. L. Burroughs, Jr., Birmingham, has been named editor of the Alabama General Practitioner, official Journal of the Alabama Academy of General Practice.

Dr. Walter B. Frommeyer, Jr., associate dean of the Medical College of Alabama, was recently appointed professor and chairman of the department of medicine.

Dr. Howard M. Phillips was recently appointed as president of the Alabama College in Montevallo.

Dr. William G. Thuss, Jr., has recently been appointed the first associate professor of industrial medicine in the department of preventive medicine and public health, Medical College of Alabama.

ARKANSAS

Dr. L. H. McDaniel of Tyronza, former councilor from Arkansas to the Southern Medical Association, will enter the United States Family Doctor of the Year contest at the American Medical Society conference at Philadelphia this December.

He won the right to participate in the national contest by being elected Arkansas State Family Doctor at the Arkansas Medical Society council meeting at Little Rock last month. He was representing Craighead-Poinsett counties.

Dr. Otis L. Anderson has recently taken over a newly-created post of assistant surgeon general of Public Health Service for personnel and training.

DISTRICT OF COLUMBIA

Dr. John J. Blasko was recently appointed chief of the Veterans Administration Psychiatry Division in the Psychiatry and Neurology Service in Washington.

The following doctors have recently been certified by the American Board of Obstetrics and Gynecology, Drs. A. B. Irani, Jr., Leon A. Martel, Jr., Seamus P. Nunan, Joseph M. O'Neil, Meyer Rosenbaum, James G. Sites, Peter Soyster, and James C. Walsh.

Dr. Melvin M. Figley's appointment as head of the University of Washington Medical School's department of radiology has been approved by the board of regents.

Colonel Joe M. Blumberg, Medical Corps, U. S. Army, Deputy Director of the Armed Forces Institute of Pathology, was recently elected vice-president of the American Society of Clinical Pathologists.

FLORIDA

Dr. David S. Howell has recently become a member of the American Physiological Society.

Dr. Dazelle Simpson was recently certified by the American Board of Pediatrics.

Dr. Robert T. Spicer, Miami, was recently elected president of the Miami-Dade County Chamber of Commerce.

Dr. Richard A. Henry, Brooksville, was recently presented a plaque by the Withlacoochee District of the Gulf Ridge Council, Boy Scouts of America, for his outstanding work with Scouts in the Brooksville area.

Dr. Douglas R. Murphy, Venice, was recently elected president of the Rotary Club of that city.

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BOOK REVIEWS

Lesions of the Cervical Intervertebral Disc

By R. Glen Spurling, M.D., Professor of Neurosurgery, University of Louisville School of Medicine, Kentucky. American Lecture Series. 116 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1956. Price $4.75.

This is a well written monograph which describes in successive chapters the history, anatomy, pathology, clinical aspects, radiographic diagnosis and treatment of cervical intervertebral disc disorders.

The author, who has long been interested in disease of the lumbar and cervical intervertebral discs, includes a review of 197 of his own selected cases. In sixty-one of these cases the diagnosis was verified by operation.

This book will be of considerable interest to all neurosurgeons, neurologists, orthopedists and other physicians who see these patients.

Cryptococcosis. Torulosis or European Blastomycosis

By M. L. Littman, M.D., Department of Microbiology, The Mount Sinai Hospital, New York; and Lorenz E. Zimmerman, M.D., Central Laboratory, Veterans Administration, Washington. 182 pages, illustrated. New York: Grune & Stratton, 1956. Price $8.50.

This monograph represents the first in an intended series of pictorial and textual treatment of the individual systemic mycoses. The authors have summarized a tremendous amount of material concerning this disease and have indexed it well. Cryptococcosis can no longer be regarded as a rarity since more than 300 cases have been reported from all parts of the world. Historical aspects of the disease are considered. The authors consider the frequency of infection with this fungus, the 25 species, and the epidemiologic significance of the isolation of the organism from soil specimens contaminated by pigeon manure.

There is an excellent description of the clinical aspects of human infections,—the localized infections, and the relationship of the respiratory tract as the portal of entry of the organisms, and the presence of focal lesions in the lung in patients with cryptococcal meningitis. Infection of the central nervous system frequently resembles other types of chronic meningitis, and the differential diagnosis, depending on whether involvement is diffuse or localized, includes such diseases as neurosyphilis, tuberculous meningitis, intracranial neoplasms, vascular thrombosis, and hydrocephalus.

Consideration is given to local involvement of the skin, mucous membranes, ocular strictures, bone, and the widespread involvement of organs including the cardiovascular system, internal genitalia, kidney, adrenal, liver, spleen, and lymph nodes.

The chapter concerned with cryptococcosis in animals suggests that infections in both man and animal is usually exogenous, probably soil-borne. The most important immunologic and histopathologic technics are discussed in detail and the pathologic changes are well documented by excellent photographs.

The treatment and prognosis of cryptococcosis is considered in a thorough fashion.

In addition to objectively and concisely summarizing the existing literature the authors have made excellent use of the collection of clinical data, pathologic material, photographs, and roentgenograms on file at the Armed Forces Institute of Pathology. This monograph is a comprehensive analysis of data concerning this disease, and in all probability will take its place as a standard reference work as more of the epidemiology and other aspects of this infection are uncovered.

Pediatric Cardiology

By Alexander S. Nadas, M.D., Assistant Clinical Professor of Pediatrics, Harvard Medical School. 563 pages. Philadelphia: W. B. Saunders Company, 1957. Price $12.00.

This book is a well-organized survey of the newer technics and concepts in pediatric cardiology. There is a comprehensive, but not too detailed or technical a discussion of acquired and congenital heart disease. The book begins with a limited discussion of the means of diagnosis, including history and physical examination, radiology, electrocardiography, phonocardiography, angiocardiography, and cardiac catheterization. Illustrations of the findings obtained by each of these studies are provided in the discussion of each condition. A helpful consideration of anesthesia for children with heart disease is presented in a separate section.

This book should prove very helpful to the pediatrician, the general practitioner, and the medical student.

Diabetes Mellitus

By Howard F. Root, M.D., Medical Director of the Joslin Clinic, Boston, and Priscilla White, M.D., Instructor in Pediatrics, Tufts University, Boston. 338 pages. New York: McGraw-Hill Book Co., Blakiston Division, 1956. Price $7.00.

A handbook, by definition, is a small book of directions. This volume serves the stated purpose well. It contains many facts that are at the "elbow" of the reader. Basic information about the etiology of diabetes is given. The dietary management is outlined clearly and the indications given for the various diet formularies, as well as methods of diet calculation.

The various available insulins are discussed, and their indications given. The use of insulin and the problem of insulin resistance, and the symptoms of hypoglycemia are reviewed.

The diagnosis of diabetic acidosis and coma and a fairly adequate summary of the essentials of treatment are listed.

Several major possible complications of diabetes are discussed such as tuberculosis, urinary tract infection, skin complications, and surgical complications. A more detailed review is given to the problem of diabetic neuropathy, eye disorders, cardiovascular and renal complications.

A rather complete and useful chapter is given to the problem of pregnancy, and to the supervision of the children of diabetic mothers.

An excellent chapter discusses the management of juvenile diabetes.

Finally a brief space is allotted to the methods of urine and blood examinations for glucose and fatty acid breakdown products, as well as the specialized determinations of the endocrine metabolic products, chorionic gonadotropin, and the urinary steroids.

Neurological Nursing. A Practical Guide

By John Marshall, M.D., M.R.C.P., M.R.C.P. ed., D.P.M., Senior Lecturer in Neurology, University of Edinburgh. Springfield, Illinois: Charles C. Thomas, Publisher, 1956. Price $3.75.

This is an attractively written volume which outlines the fundamental procedures in the nursing care of neurological patients. Although this is a practical guide, the author has not omitted an adequate consideration of the underlying principles.

Such topics as the prevention and treatment of pressure sores, the management of neurological disorders of the bladder, nursing the comatose patient, rehabilitation, the management of epilepsy and various neurodiagnostic technics are well presented.

This book should be of considerable benefit to all nurses, social workers, physical therapists and other personnel who assist in the care of neurological patients. There is much here which would be of interest to physicians and medical students as well. It is highly recommended.

Basic Foundations of Isotope Technique for Technicians

Edited by Willard C. Smullen, M.D., Radiologist in Charge, St. Mary's Hospital, Decatur, Illinois. 152 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1957. Price $4.75.

The increased use of radioisotopes in the medical school, hospital, and research institute has resulted in a need for an increased number of trained personnel at the level of the medical laboratory or x-ray technician. This book was written primarily for people with this type of background training. For those who desire more detailed and technical information, bibliographies are presented at the end of some chapters.

Three chapters contain material of a basic nature necessary in understanding the principles and methods of application of radioisotopes. These are: "Physical Foundations of Radioactivity" by J. S. Durlacher, "Radiation Measuring Instruments" by J. P. Aldworth, and "Elements of Protection" by G. W. Morgan. The chapter by Durlacher is a short one presenting brief discussions of atomic structure, types of isotopes, emission of alpha and beta particles and of gamma rays, and units of radioactivity measurements. The chapters describing radiation measuring instruments includes different types of Geiger tubes, scintillation detectors, scalers, count-rate meters, and portable units for monitoring. It is well illustrated with photographs and is written in a nontechnical manner. The article by Morgan presents a brief but adequate basic discussion on principles of radiation protection.

The material which follows deals with applications of various isotopes to medical problems. J. W. Little in "The Diagnostic Use of Radioiodine" describes in detail the procedure of performing a 24-hour I^{131} uptake study. Uses of I^{131} therapeutically are reviewed briefly by W. C. Smullen. Similar material on radiophosphorus and on radiogold is described by Glenn E. Ross and Edward Cook, respectively.

The two final chapters are by D. L. Tabern. The first of these describes several analytical procedures using radioisotopes, including plasma volume studies with I^{131}-labeled serum albumin, red cell labelling with Cr^{51}, and pernicious anemia studies with Co^{60}-labeled vitamin B_{12}. The last chapter lists various radio pharmaceuticals available and the licensing procedure needed for procurement of these items.

Among several items included in an appendix are a glossary and decay curves for P^{32}, I^{131}, and Au^{198}.

This book should be helpful to technicians desiring or needing training in the handling of radioisotopes. The material published in this book is based upon a series of lectures given at one of the first radioisotope courses for technicians in the United States. The technician reading this book should realize that it is as important to undertake supervised laboratory work in handling radioisotopes as it is to read books if one actually wants to master these technics.

In an introduction to the book Paul C. Aebersold, formerly Director, Isotopes Extension, Division of Civilian Application, Oak Ridge, said: "The amount of training the technician should acquire depends on the size of the program with which he will be associated and the responsibility which he will have. Technicians will find interesting opportunities awaiting them in this new, expanding field provided they are willing to obtain sufficient training in technics and safe handling of radioisotopes."

Diseases of the Heart and Circulation

By Paul Wood, O.B.E., M.D., F.R.C.P., Director, Institute of Cardiology, London. Second, revised and enlarged edition, 947 pages. Philadelphia: J. B. Lippincott Company, 1956. Price $15.00.

This book would make a useful addition to every practicing physician's library and should prove valuable as a textbook for undergraduate students. The subject matter is well organized, avoiding excessive repetition, and is presented with a moderate degree of dogmatism rather than expressing controversial opinions. References are adequate to support the views expressed and are up through 1955. An occasional term which is not commonly used in this country, such as "skiagram" (roentgenogram) or "trinitrin" (nitroglycerine), reminds the reader that the author is not American. Among many strong points are the discussions concerning bedside physical

diagnosis, cardiovascular disturbances associated with psychiatric states and recent advances in therapy, particularly cardiac surgery. The author is to be commended for his excellent work.

Epilepsy. Grand Mal, Petit Mal, Convulsions

By Letitia Fairfield, C.B.E., M.D., D.P.H. 159 pages. New York: Philosophical Library, Inc., 1957. Price $4.75.

This volume has been written primarily for the public and is a very lucid exposition of the problem of epilepsy. The author includes an introductory section about the history and nature of the disease followed by chapters on treatment, the epileptic child, and the relevant social and medical problems concerning employment, schooling, marriage and the law.

Although many of the administrative aspects refer to the situation in Great Britain, this book will be of value to all nurses, social workers and other nonmedical personnel who have an interest in patients with epilepsy.

Fundamentals of Clinical Neurophysiology

By Paul O. Chatfield, M.D., Formerly Assistant Professor of Physiology, Harvard Medical School. 358 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1957. Price $8.50.

This is a scholarly monograph which includes a detailed consideration of such basic concepts as membrane potential and nerve impulse, synaptic transmission, and physiology of muscle. The author has wisely selected such subjects as the nervous control of breathing, postural coordination, physiology of the vestibular apparatus, and the neurophysiology of the special senses for further discussion. There is an impressive array of references on each of these subjects.

This work will be of great benefit to physicians pursuing graduate training in the neurologic specialties, and it will serve as an excellent refresher course for clinicians who have not been able to keep abreast of the large volume of literature relating to neurophysiology. It is highly recommended.

Modern Therapy in Neurology

Edited by Francis M. Forster, M.D., Dean and Professor of Neurology, Georgetown University School of Medicine, Washington, D. C. 754 pages. St. Louis: C. V. Mosby Co., 1957. Price $12.00.

This book is an admirable refutation of the thesis that neurology is a clinical specialty devoted to diagnosis rather than treatment. The editor has assembled a very able group of experienced clinicians as contributors to this pioneer volume.

The treatment of meningitis, encephalomyelitis, epilepsy, myasthenia gravis, neurosyphilis and headache are considered in detail. There are also sections on the management of patients with cerebrovascular disease, degenerative neurologic disorders, demyelinating diseases, and metabolic diseases of the nervous system. Adequate attention is devoted to the rehabilitation of the neurologic patient, and there is a chapter on the use of tranquilizing drugs in neurology.

This treatise will be of inestimable value to internists and practitioners and is highly recommended to all physicians who see patients with neurologic disorders.

Principles and Methods of Sterilization

By John J. Perkins, M.S., Director of Research, American Sterilizer Company, Erie, Penn. 334 pages, illustrated. Springfield, Illinois: Charles C. Thomas, Publisher, 1956. Price $8.00.

The author of this book is the Director of Research of the American Sterilizer Company. In the preface he states that the book is an attempt to integrate the basic principles upon which sterilization depends with practical methods for preparation and sterilization of materials and supplies. The volume is presented as a practical guide within textbook limits, rather than a reference volume. I feel that he has succeeded in his efforts.

The first chapter is a rather extensive historical review of the entire subject, which I found particularly interesting. The author covers the rather technical subjects of thermal destruction of bacteria, principles of steam sterilization, and minimum standards of sterilization very well and makes them understandable, especially the principles and workings of the steam sterilizer. In later chapters, he deals with water sterilizers, dry heat sterilization, disinfection with boiling water, and chemical disinfection. He emphasizes the limitations of each method.

In the chapters on preparation and sterilization of the various supplies, he stresses the importance of

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INSTRUCTIONS TO CONTRIBUTORS

Exclusive Publication: Articles offered for publication must be contributed solely to the Southern Medical Journal.

Manuscripts: Manuscripts should be original copy, typewritten, double-spaced, with wide margins. Footnotes and references should conform to the following style:

1. Doe, J. E.: What You Should Know about It, New England J. Med. 243:435, 1950.

Illustrations: Black and white glossy prints, preferably 5 by 7 inches, and drawings in India ink on white paper are required. The author's name, number and indication of top, if doubtful, should be attached. Necessary plates not exceeding six, or one and a half pages, will be furnished by the Journal.

Reprints: Reprints are available at publisher's cost. An order form will accompany author's galley proof and should be returned with the galley to the Editor.

Book Reviews: Books and monographs submitted for review should be mailed to the Editor. Acknowledgment will appear in the Journal. Selection rights reserved.

Editorial Address: All manuscripts, corrected galley proof, reprint orders, books for review and related correspondence should be addressed to the Editor, R. H. Kampmeier, M.D., Vanderbilt University School of Medicine, Nashville 5, Tennessee.

Business Address: All correspondence related to membership, subscriptions, advertising, and other business should be addressed to the Southern Medical Association, Empire Building, Birmingham 3, Alabama.

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BOOK REVIEWS

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proper placement of articles in the packs and proper placement of the packs in the sterilizer. His chapter on the setting up and running of a central supply department are particularly valuable. There are also chapters on the preparation and sterilization of parenteral solutions, the preparation of infant formulas, the laboratory autoclave, and the newer method of gaseous sterilization with ethylene oxide. Throughout the book, Mr. Perkins shows that he is not unaware of institutional financing. He frequently points out ways to increase efficiency and decrease cost.

After reading this book I reread Dr. Carl Walter's *Aseptic Treatment of Wounds*. While the book being reviewed does not replace Dr. Walter's book, it is a valuable companion volume. I believe that an operating room or central supply supervisor would do well to have a copy available, since it is a book that their personnel can read and understand. Lastly, since most physicians are unfamiliar with the problems of sterilization, I believe that most of us could profitably read this book.

Handbook on Poliomyelitis

By Joseph Trueta, M.D., D.Sc. (Hon.) (Oxon.), F.R.C.S. Nuffield Professor of Orthopaedic Surgery, University of Oxford; A. B. Kinnier Wilson, M.A., M.B., M.R.C.P., D.P.M.; and Margaret Agerholm, M.A., B.M., B.Ch. (Oxon.) 135 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1957. Price $3.75.

This handbook has been written primarily for the practitioner. It is a readable account of the epidemiology, pathogenesis, pathology, semeology, and management of poliomyelitis. The chapter on the clinical aspects and diagnosis will be helpful to the physician who does not have an adequate experience with this disease. In the opinion of this reviewer, the authors' reluctance to dismiss electrical stimulation of involved muscles as a means of therapy contrasts strangely with their dogmatic assertion that lumbar puncture is contraindicated in poliomyelitis. This volume represents no signal advance over others dealing with the same subject.

Six Children

By Estelle J. Foote, M.D., Psychiatrist in Charge, Traveling School Clinic, Walter E. Fernald State School, Waverly, Mass. 311 pages. Springfield, Illinois: Charles C. Thomas, Publisher, 1956. Price $5.50.

In the words of the author, "this book is for those who are interested in children and who study them because they wish to help them."

Dr. Foote has compiled this volume out of her careful study of over thirty-six hundred children studied in the Traveling School Clinic in the Commonwealth of Massachusetts. The author is Psychiatrist in Charge of this Clinic. The material has been supplemented by the examination of children in the Walter E. Fernald State School, Waverly, Massachusetts, and an occasional child examined before the court. The author has very carefully grouped these children into six sections, namely: The Quick Thinking Child, The Slow Thinking Child, The Child Whose Brain Has Been Injured, The Child Maladjusted Emotionally, The Child of Unusual Cultural Background, and The Child of Unusual Training.

A supplemental chapter has been added dealing with the child with an unusual physical defect, and the child called delinquent. In examining these children the author has taken full account of the family history, the child's characteristics as seen by the parent, the school history, his characteristics as seen by the teacher and an accurate appraisal of his academic achievement in each school subject. In addition, psychometric studies and psychiatric interviews are reported. The chapters close with case studies, differential diagnosis, a general discussion of the problem and sound, practical advice.

At the conclusion of the book, samples of all the charts and forms used in the study are included.

This volume is a welcome addition to the library of psychiatrists, pediatricians and general practitioners. It would also be of great value to teachers, supervisors, principals and superintendents of schools who have a sincere and abiding interest in the children presented to them for education, particularly that this latter group might better understand children who seem to fall somewhat outside the latitudes of the so-called normal child, but who have great potential if they can be understood.

For the practitioner who wishes to delve deeply and intensively into a child with a special problem, additional references would be necessary, but for a general picture of the types of children listed above and sound advice as to their understanding and management, the volume is to my knowledge unsurpassed.

It is original, authoritative and extremely practical.

The Office Assistant in Medical or Dental Practice

By Portia M. Frederick and Carol Towner. 336 pages. Philadelphia: W. B. Saunders Company, 1956. Price $4.75.

Though this book is of benefit to anyone working as a medical assistant or such aides as hospital admitting personnel or workers in health agencies, etc., its primary purpose is for the assistant working directly with or for a physician or dentist.

Many items are presented in an informative manner regarding bookkeeping, banking, billing and collections, insurance matters, preparation of manuscripts, and actual nursing duties. For the nurse or aide, directly assisting the doctor, there are sections on care of instruments for office and doctor's bag, preparation of medications, immunizations, injections and physical therapy. For all types of office assistants one thing which is stressed and is of importance is the handling of patients properly and making them feel at ease.

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Continued from page 1541

GEORGIA

Dr. Trawich H. Stubbs was recently appointed director of the mental hygiene division, Georgia Department of Public Health.

Dr. W. W. Hills, Sr., Sardis, was recently honored at a special service at the Sardis Baptist Church in recognition of his contributions to the growth and progress of the community during his 47 years of medical service there.

Dr. E. W. Waldemayer, Americus, was recently named county physician of that city.

Dr. Ed T. Arnold, Hogansville, was recently named one of the editors of the national publication "Medical Digest."

Dr. Ted F. Leigh, Atlanta, was recently elected president of the Atlanta Radiological Society. Other officers include Dr. John O. Ellis as vice-president, and Dr. J. Luther Clements as secretary-treasurer.

Dr. Y. Harris Yarbrough, Milledgeville, was recently honored by a surprise birthday party given by the staff of the Milledgeville State Hospital.

Dr. Hart S. Odom, LaFayette, was recently elected as the new district medical director for the four counties of Catoosa, Dade, Walker, and Catooga.

Dr. A. F. Routledge, Rome, was recently named temporary secretary-treasurer of the newly formed

Continued on page 52

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Continued from page 50

board of directors for the North Georgia Clinic for the Crippled.

Dr. David E. Tanner, Marietta, has recently joined Dr. W. H. Mathis, Jr., as associate in radiology at Kennestone Hospital.

Dr. Ernest R. Harris, Winder, recently received a 5 year pin and a certificate of distinction for service to his profession by the Medical Association of Georgia.

Dr. G. Lombard Kelley, Augusta, was recently voted a charter member of the newly organized Society for the Scientific Study of Sex.

Dr. Relliford S. Smith, Macon, was recently elected as president-elect of the National Medical Association.

Continued on page 70

NEXT MEETING

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NOV. 3-6, 1958

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Cardiology	December 2-6, 1957
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Rhinoplastic Surgery	February 3-8, 1958
Pediatric Orthopedics	February 24-28, 1958
Vascular Surgery (by invitation)	March 24-28, 1958
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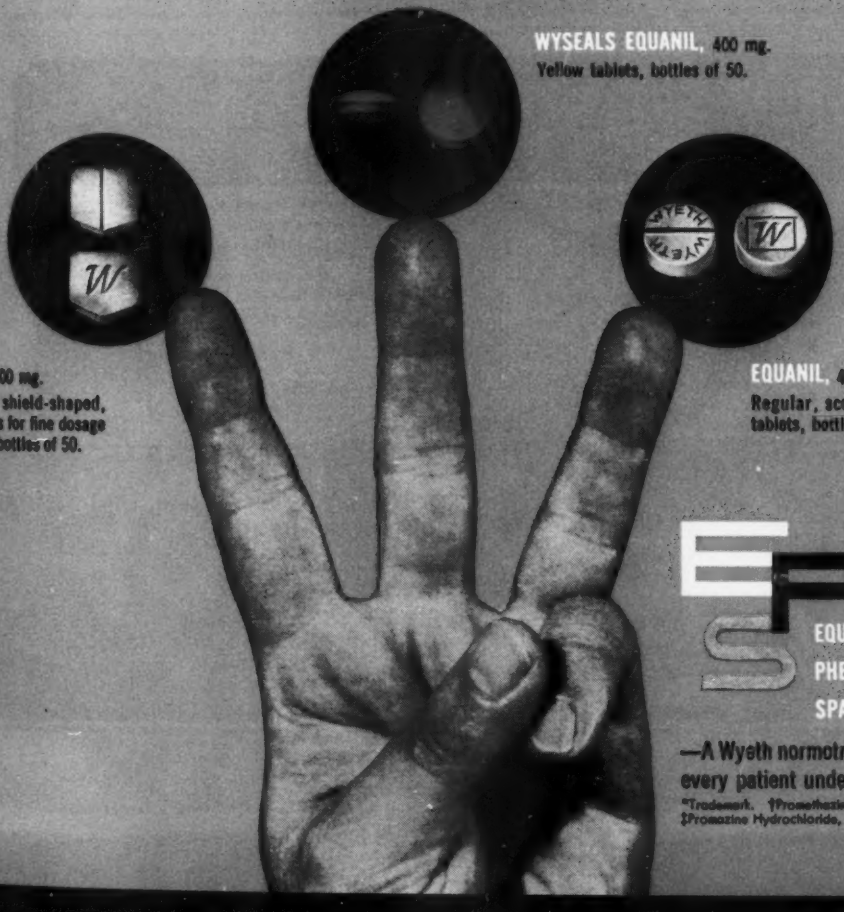

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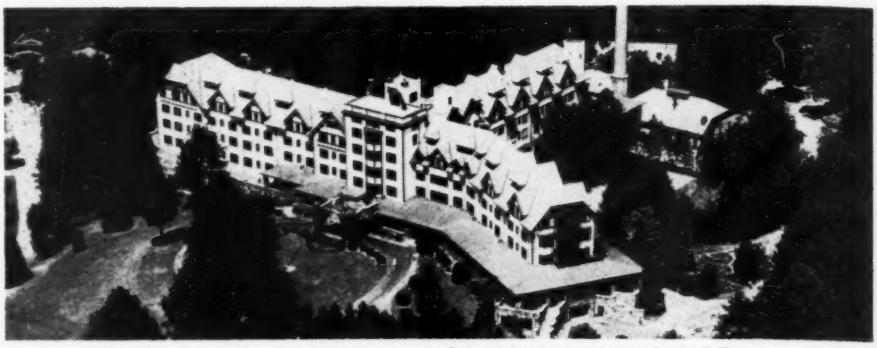

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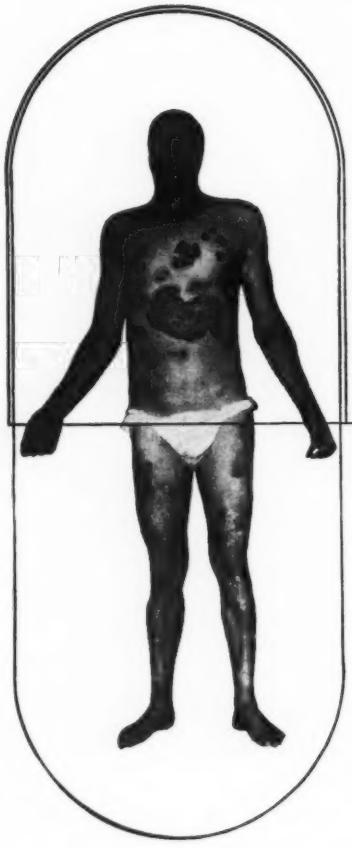

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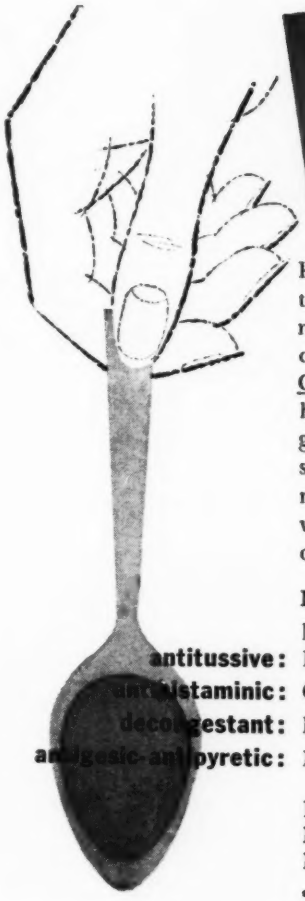

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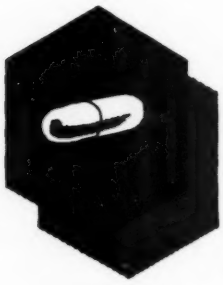

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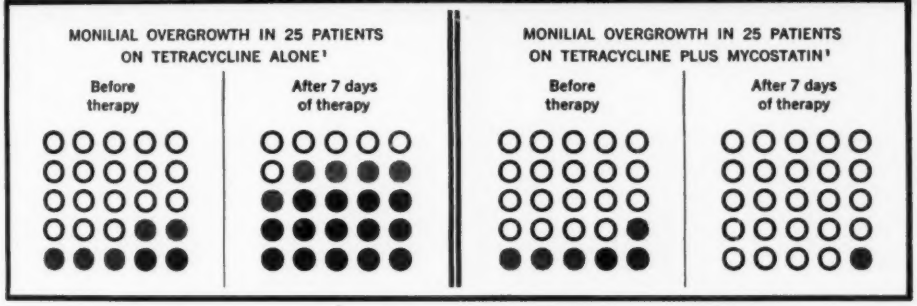

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1. Childs, A. J.: British M. J. 1:660 (March) 1956.

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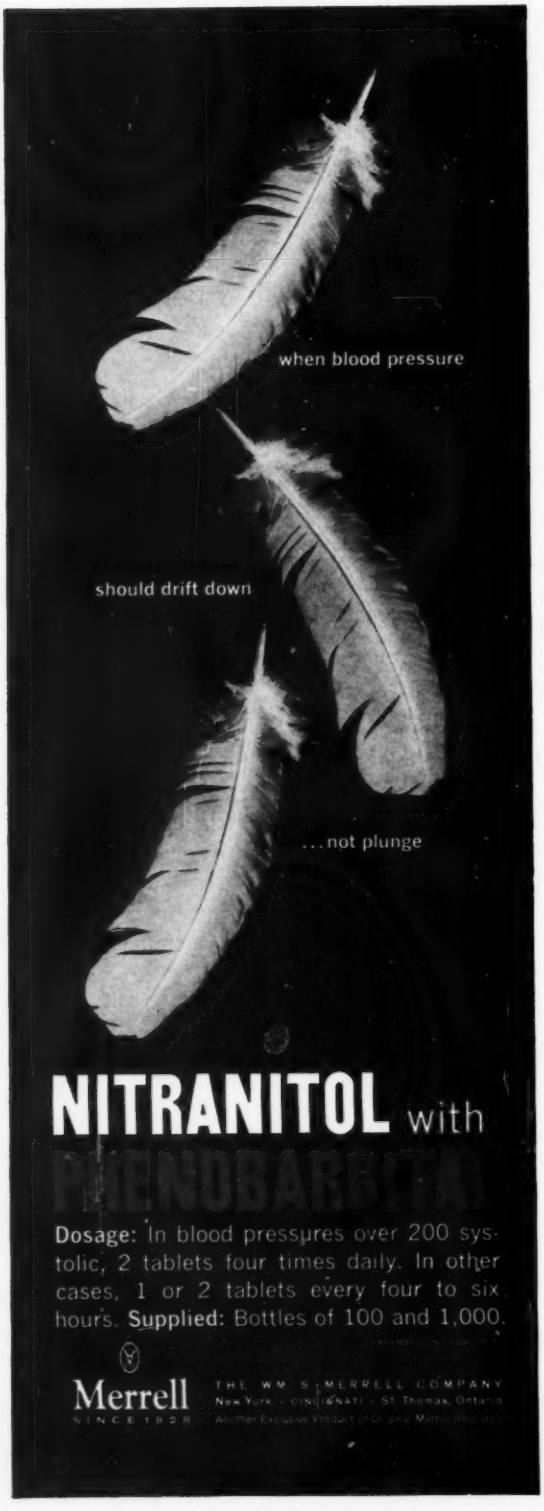
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NEW ORLEANS ACADEMY OF OPHTHALMOLOGY

The Eighth Annual meeting of the New Orleans Academy of Ophthalmology will be held in New Orleans in the Roosevelt Hotel—February 24-28, 1958, featuring "Symposium on Uveitis." The registration fee of $75.00 includes associate membership in the Academy for the year of 1958, as well as all other features of the convention. Hotel reservations should be made early by writing directly to the Executive Secretary, P. O. Box 469, New Orleans, Louisiana.

Lederle mumps vaccine

effective
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A specific immunizing antigen for prevention of mumps in children and adults where indicated. Vaccination should be repeated annually.

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Blood pressure in obese hypertensives frequently drops with weight loss[1]

And when an appetite-curbing agent is necessary to help bring about weight loss in obese hypertensives, many physicians prefer 'Dexedrine' because it has little or no pressor effect in the usual dosages.[2]

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1. Ferguson, H.E.: Virginia M. Monthly 76:222
2. Roberts, E.: Am. Pract. & Dig. Treat. 5:608

*T.M. Reg. U.S. Pat. Off.

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IN ACNE, Fostex Cream and Fostex Cake

- **degrease, peel and degerm the skin**
- **unblock pores . . . help remove blackheads**
- **help prevent pustule formation**
- **minimize spread of infection**

Fostex effectiveness is provided by Sebulytic® (sodium lauryl sulfoacetate, sodium alkyl aryl polyether sulfonate, sodium dioctyl sulfosuccinate) a new combination of surface active cleansing and wetting agents with remarkable antiseborrheic, keratolytic and antibacterial action, enhanced by sulfur 2%, salicylic acid 2% and hexachlorophene 1%.

Fostex is easy to use. The patient stops using soap on acne skin and starts washing with Fostex. Effective and well tolerated... assures patient acceptance and cooperation.

FOSTEX CREAM for therapeutic washing of the skin in the initial phase of the treatment of acne, when maximum degreasing and peeling are desired.

in 4.5 oz. jars

FOSTEX CAKE for maintenance therapy to keep the skin dry and substantially free of comedones.

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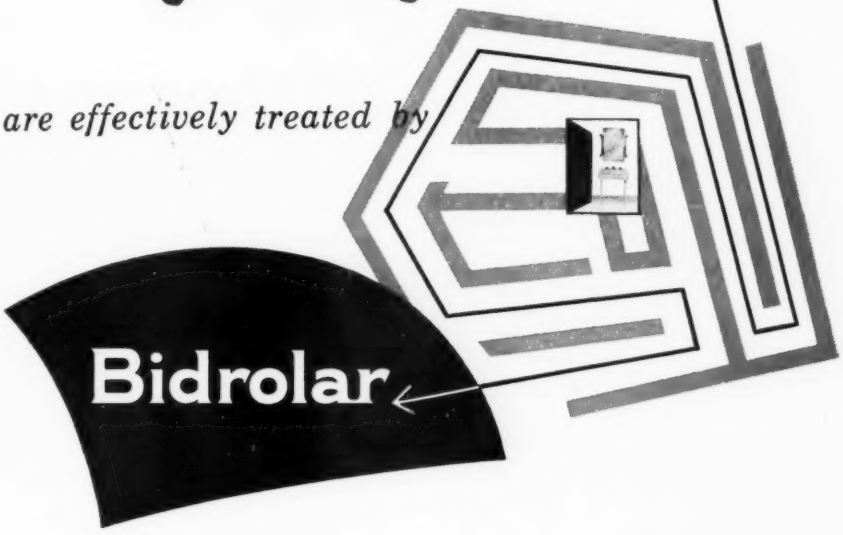
victims of

fecal frustration

are effectively treated by



Bidrolar combines a natural laxative with an effective stool softener. It provides effective combination therapy without the use of irritating bowel evacuants and without the disadvantages and lack of peristaltic action noted with the use of stool softeners alone.

Each Bidrolar tablet provides **ox bile,** 60 mg.—a peristaltic stimulant that produces natural laxation without irritating the bowel . . . and **dioctyl sodium sulfosuccinate,** 40 mg.— an effective stool softener that keeps feces soft for easy evacuation.

in fecal frustration **Bidrolar** *is* ***naturally*** *better*

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CHOLOGESTIN contains both ox bile extract and sodium salicylate, plus pancreatin and sodium bicarbonate. Recommended dose as a choleretic or cholagogue, 1 tablespoonful in cold water after meals.

TABLOGESTIN, 3 tablets are equivalent to 1 tablespoonful of Chologestin.

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Please send me free sample of TABLOGESTIN together with literature on CHOLOGESTIN.

DR.....

STREET.....

CITY.....ZONE.....STATE.....

Continued from page 52

KENTUCKY

Dr. Gant Gaither was recently honored by the Hopkinsville Rotary Club at a special program paying tribute to his contribution to the betterment of the community.

Dr. Robert Guy Blackwelder was recently named superintendent of Western State Hospital at Hopkinsville.

Dr. Dixon R. McCloy recently joined the staff of the Graves-Gilbert Clinic in Bowling Green, where he will limit his practice to general surgery.

Dr. Lewis W. Cochran has succeeded Dr. Lyle R. Dawson as University of Kentucky representative to the ORINS Council.

LOUISIANA

Dr. M. Atik has recently been named instructor in surgery at the Louisiana State University School of Medicine.

Dr. C. A. McMahan has recently been named associate professor (biostatistics) department public health and preventive medicine.

Dr. Lyon K. Loomis recently received a gold trophy representing the highest award given in photography by the American Physicians Art Association.

Continued on page 72

Hydrolamins®

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for:

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Pruritus Vulvae

Pinworm Pruritus

Diaper Rash

Lewal PHARMACEUTICAL COMPANY
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release from anxiety

ULTRAN

(Phenaglycodol, Lilly)

. . . helps restore normal emotional composure without impairing mental acuity

Dosage:
Usually 1 pulvule t.i.d.

Supplied:
As attractive turquoise-and-white pulvules of 300 mg.

'Ultran' quickly allays anxiety and tenseness. Broadly evaluated under carefully controlled conditions, 'Ultran' has been shown to be unusually safe. There are no contraindications. It is chemically unique—not related to any other tranquilizer.

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when blood pressure
should drift down
...not plunge
NITRANITOL with
PHENOBARBITAL
Dosage: In blood pressures over 200 systolic, 2 tablets four times daily. In other cases, 1 or 2 tablets every four to six hours. Supplied: Bottles of 100 and 1,000.
Merrell
SINCE 1828
THE WM. S. MERRELL COMPANY
Another Exclusive Product of Original Merrell Research

Continued from page 70

MARYLAND

Dr. Robert D. Coghill has recently been appointed special assistant for Industrial research at the Cancer Chemotherapy National Service Center, National Cancer Institute.

Dr. Joseph L. Melnick has recently been appointed to the staff of the Division of Biologics Standards, National Institutes of Health.

Dr. Henry Bearden Mulholland has recently accepted membership on the National Advisory Arthritis and Metabolic Diseases Council.

MISSOURI

Dr. Armand E. Brodeur has recently been named assistant dean of the School of Medicine at the Saint Louis University.

Dr. Walter R. Jordan has recently been appointed acting director, Division of Health and Hygiene of the Board of Education.

Dr. Gerald J. Malloy, assistant administrator, St. John's Hospital, was recently named executive director of Greater St. Louis Hospital Council.

Drs. Edmund F. Sassin and Powell B. McHaney, St. Louis, have recently been appointed by Governor Blair as members of the State Mental Health Commission.

Dr. I. R. Davis Day was recently honored at the St. Louis Medical Society's Fall Golf Tournament.

Continued on page 74

CITY VIEW
SANITARIUM

For the diagnosis and treatment of nervous and mental disorders, and addiction to alcohol and drugs.

Established 1907

NASHVILLE, TENNESSEE

when anxiety must be relieved

'Compazine' controls anxiety and tension —rapidly and with minimal side effects.

Most patients on 'Compazine' are not lethargic or logy. They carry out their normal activities unhampered by drowsiness and depressing effect.

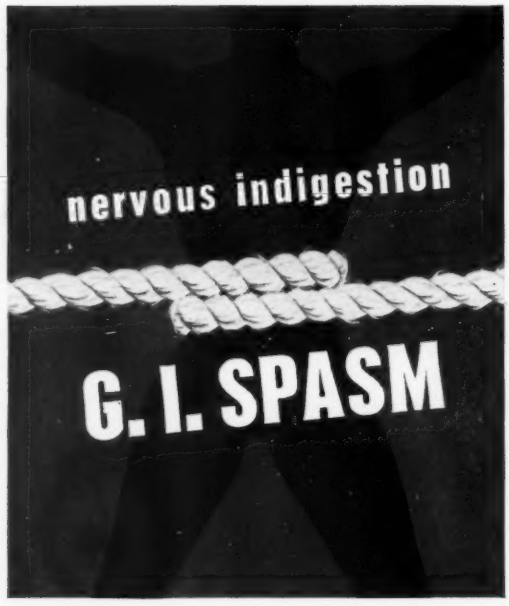
Compazine★

the tranquilizer remarkable for its freedom from drowsiness and depressing effect

available:
Tablets, Ampuls and Spansule® sustained release capsules

Smith, Kline & French Laboratories, Philadelphia

★T.M. Reg. U.S. Pat. Off. for prochlorperazine, S.K.F.



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Fortified Digestive Enzymes

WITH ANTISPASMODIC

Convertin-H fortifies gastric and pancreatic enzymes to aid digestion, and supplies an effective antispasmodic to combat the spasm.

Composition:
Each Convertin-H tablet contains:

In sugar-coated outer layer
Homatropine Methylbromide.....2.5 mg.
Betaine Hydrochloride.....130.0 mg.
(providing 5 minims diluted Hydrochloric Acid U.S.P.)
Oleoresin Ginger.....1/600 gr.

In enteric-coated inner core
Pancreatin (4 x U.S.P.).....62.5 mg.
(equiv. to Pancreatin U.S.P. 250 mg.)
Desoxycholic Acid.....50.0 mg.

Dose: 1 or 2 tablets with or just after meals.

Supplied: In bottles of 84 and 500 tablets.

send for samples

B. F. Ascher & Co., Inc.
Ethical Medicinals
KANSAS CITY, MO.

Continued from page 72

Dr. Norman Tobias, St. Louis, recently returned from the Far East where he lectured before the Tokyo, Bangkok, and Manila Medical Societies under the auspices of the World Medical Association.

Dr. Robert M. Matthews, Kansas City, was recently awarded an all expense trip to the September meeting of the International College of Surgeons in Chicago.

Dr. U. C. Weston, Galt, was recently honored for his 47 years of service to this city.

Dr. E. Lee Dorsett has been invited to deliver a lecture before the students of the Medical of Haiti at Port-au-Prince the latter part of November.

Drs. Walter T. Gunn and Robert B. Bassett, St. Louis, have recently been elected as directors of the Mississippi Valley Medical Society.

Dr. William E. Henrickson, Poplar Bluff, was recently elected for a 1 year term as a director of the Mississippi Valley Medical Society.

Dr. Ralph Ferguson, Joplin, was recently elected as medical representative to the 13th district of the Missouri division of the society.

Dr. George Q. Dunmire, Kennett, was recently appointed to the board of trustees of the Dunklin County Health Center.

Dr. John Earl Smith, St. Louis, recently received the 1957 W. Scott Johnson Award of the Missouri Public Health Association for "distinguished service in public health" in the state.

Continued on page 81

MAGNETIC REMOVAL OF FOREIGN BODIES

By

MURDOCK EQUEN, M.D., F.A.C.S.
Founder and Chief of Staff of Ponce de Leon Infirmary Atlanta, Georgia

The Use of the Alnico Magnet in the Recovery of Foreign Bodies from the Air Passages, the Esophagus, Stomach and Duodenum.

Written in an *informal, conversational style* and abundantly illustrated with roentgenograms, this book can be read with interest by many groups, especially bronchoscopists, pediatricians, general practitioners, gastroenterologists, otolaryngologists, roentgenologists and chest surgeons.

- Describes and illustrates the various modifications the author has made in the original Alnico magnet and the auxiliary apparatus, often of his own design, that he has used
- Describes the author's **technics**
- Discusses **roentgenologic diagnosis**, including **some original pointers**
- Points out **disadvantages, contraindications** and **precautions.**

104 pages 119 illustrations
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you too will
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for monilial vaginitis
it works when others fail

0.1% gentian violet vaginal anti-infective in acid polyethylene glycol base.
12 single dose disposable plastic applicators.

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CLIMATE AIDS IN THERAPY
SUNSHINE 360 DAYS OF THE YEAR!

ANCLOTE MANOR
A MODERN HOSPITAL FOR EMOTIONAL READJUSTMENT
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ON THE GULF OF MEXICO

● Modern Treatment Facilities ● Psychotherapy Emphasized ● Large Trained Staff ● Individual Attention ● Capacity Limited ● Occupational and Hobby Therapy ● Supervised Sports ● Religious Services Plus . . .

Your patients spend many hours daily in healthful outdoor recreation, reviving normal interests and stimulating better appetites and stronger bodies . . . all on Florida's Sunny West Coast.

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Consultants in Psychiatry
SAMUEL G. WARSON, M.D. ROGER E. PHILLIPS, M.D
WALTER H. BAILEY, M.D.

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CYANOCOBALAMIN (CRYSTALLINE VITAMIN B_{12})

When appetites lag, REDISOL as a dietary supplement will often stimulate new interest in food. Weight gain follows increased food intake. Cherry-flavored REDISOL Elixir and soluble REDISOL Tablets readily mix with liquids.

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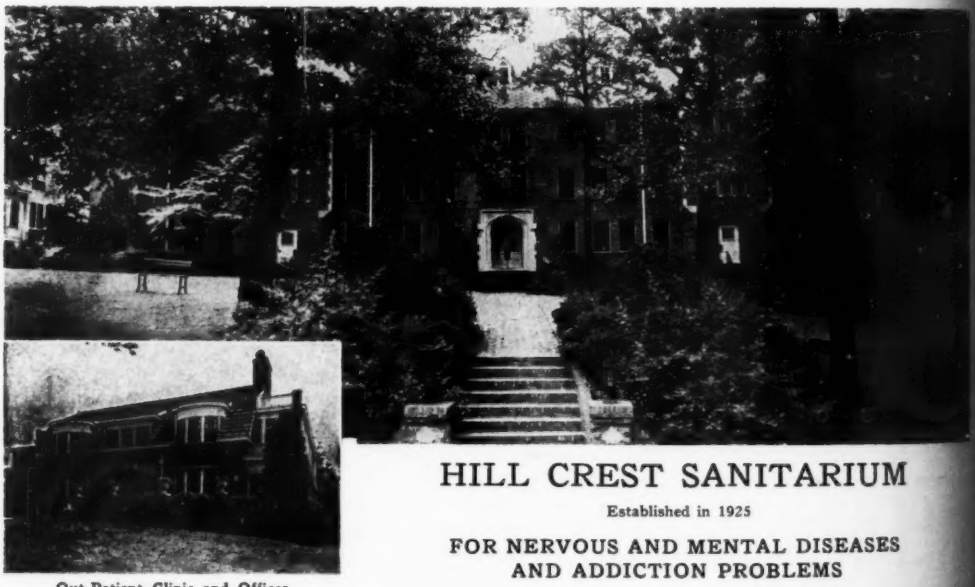

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FOR NERVOUS AND MENTAL DISEASES
AND ADDICTION PROBLEMS

James A. Becton, M.D. James Keen Ward, M.D.

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now combined: muscle relaxant and analgesic

FLEXILON

links FLEXIN* Zoxazolamine† "...a valuable lissive agent in voluntary muscle spasm of spinal or orthopedic origin"[1]

with TYLENOL* Acetaminophen, an effective analgesic for the treatment of musculoskeletal conditions.[2]

In common orthopedic and rheumatic conditions, FLEXILON promptly and safely relaxes spasm of the skeletal muscle and relieves pain.

supplied: Tablets, enteric coated, orange, bottles of 50. Each tablet contains FLEXIN, 125 mg., and TYLENOL, 300 mg.

and when a steroid is indicated...

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(FLEXIN + TYLENOL + Hydrocortisone)

provides the anti-inflammatory benefits of hydrocortisone with the spasmolytic and analgesic effects of FLEXILON.

supplied: Tablets, enteric coated, pink, bottles of 36. Each tablet contains: FLEXIN, 125 mg.; TYLENOL, 300 mg.; and Hydrocortisone, 2.5 mg.

references: (1) Settel, E.: Am. Pract. & Digest Treat. *8*:443, 1957.
(2) Batterman, R. C., and Grossman, A. J.: Federation Proc. *14*:316, 1955.

*Trade-mark
†U. S. Patent Pending

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is the **symbol**
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Standardized
Tablets
Quinidine Sulfate
Natural
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By specifying the name, the physician will be assured that this standardized form of Quinidine Sulfate Natural will be dispensed to his patient.

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For the treatment of
NERVOUS AND
MENTAL DISEASES

Ground 600 Acres — Buildings, Brick
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Site High and Healthful

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Terms Reasonable

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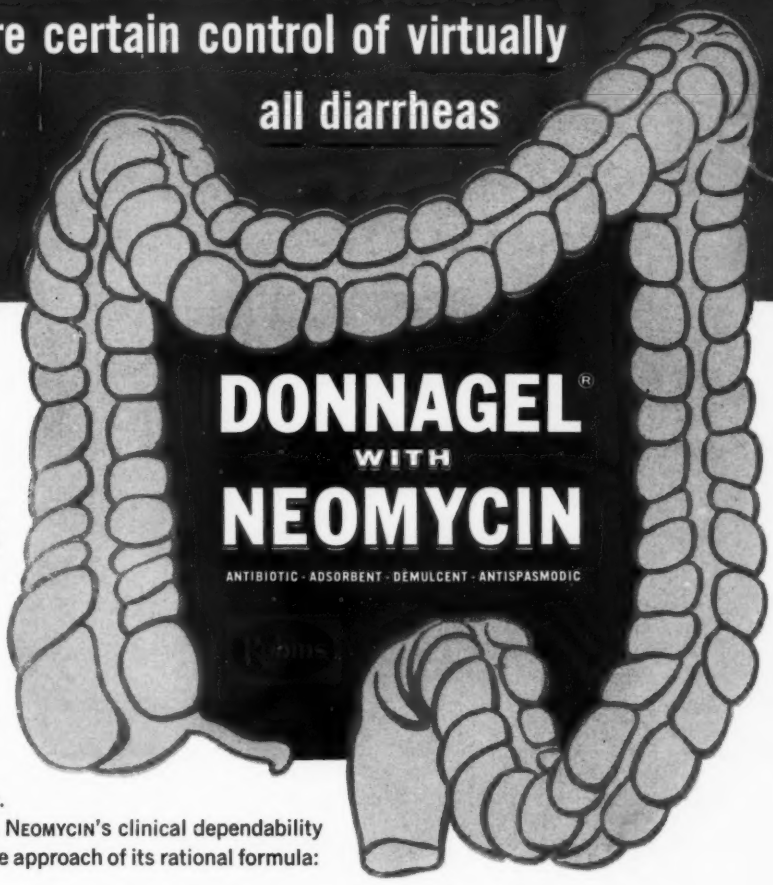
ANNOUNCING: a NEW antidiarrheal for

more certain control of virtually all diarrheas



Addition of neomycin to the effective DONNAGEL formula assures even more certain control of most of the common forms of diarrhea. Neomycin is an ideal antibiotic for enteric use: it is effectively bacteriostatic against neomycin-susceptible pathogens; and it is relatively non-absorbable.

The secret of DONNAGEL WITH NEOMYCIN's clinical dependability lies in the comprehensive approach of its rational formula:

COMPONENT in each 30 cc. (1 fl. oz.)	ACTION	BENEFIT
Neomycin base, 210.0 mg. (as neomycin sulfate, 300 mg.)	antibiotic	Affords effective intestinal bacteriostasis.
Kaolin (6.0 Gm.)	adsorbent, demulcent	Binds toxic and irritating substances. Provides protective coating for irritated intestinal mucosa.
Pectin (142.8 mg.)	protective, demulcent	Supplements action of kaolin as an intestinal detoxifying and demulcent agent.
Dihydroxyaluminum aminoacetate (0.25 Gm.)	antacid, demulcent	Enhances demulcent and detoxifying action of the kaolin-pectin suspension.
Natural belladonna alkaloids: hyoscyamine sulfate (0.1037 mg.) atropine sulfate (0.0194 mg.) hyoscine hydrobromide (0.0065 mg.)	anti-spasmodic	Relieves intestinal hypermotility and hypertonicity.
Phenobarbital (¼ gr.)	sedative	Diminishes nervousness, stress and apprehension.

Robins

Informational literature available upon request.

INDICATIONS: DONNAGEL WITH NEOMYCIN is specifically indicated in diarrheas or dysentery caused by neomycin-susceptible organisms; in diarrheas not yet proven to be of bacterial origin, prior to definitive diagnosis. Also useful in enteritis, even though diarrhea may not be present. **SUPPLIED:** Bottles of 6 fl. oz. At all prescription pharmacies.

DOSAGE: Adults: 1 to 2 tablespoonfuls (15 to 30 cc.) every 4 hours. **Children over 1 year:** 1 to 2 teaspoonfuls every 4 hours. **Children under 1 year:** ½ to 1 teaspoonful every 4 hours.

ALSO AVAILABLE: DONNAGEL, the original formula, for use when an antibiotic is not indicated.

A. H. ROBINS CO., INC., RICHMOND 20, VA.

ANNOUNCING

The Twenty-First Annual Meeting

of

THE NEW ORLEANS GRADUATE MEDICAL ASSEMBLY

Conference Headquarters—Roosevelt Hotel

March 3, 4, 5, 6, 1958

GUEST SPEAKERS

Carleton B. Chapman, M.D., Dallas, Tex.
Cardiology

Herbert Rattner, M.D., Chicago, Ill.
Dermatology

Charles A. Flood, M.D., New York, N. Y.
Gastroenterology

Robert A. Davison, M.D., Memphis, Tenn.
General Practice

Lawrence M. Randall, M.D., Rochester, Minn.
Gynecology

Bayard T. Horton, M.D., Rochester, Minn.
Internal Medicine

Perrin H. Long, M.D., Brooklyn, N. Y.
Internal Medicine

George N. Raines, Capt., MC, USN, Washington, D. C.
Neuropsychiatry

Robert H. Barter, M.D., Washington, D. C.
Obstetrics

Ralph O. Rychener, M.D., Memphis, Tenn.
Ophthalmology

C. Leslie Mitchell, M.D., Detroit, Mich.
Orthopedic Surgery

Frank D. Lathrop, M.D., Boston, Mass.
Otolaryngology

Arthur H. Wells, M.D., Duluth, Minn.
Pathology

James Marvin Baty, M.D., Boston, Mass.
Pediatrics

Harold O. Peterson, M.D., Minneapolis, Minn.
Radiology

Jere W. Lord, Jr., M.D., New York, N. Y.
Surgery

Claude E. Welch, M.D., Boston, Mass.
Surgery

Ormond S. Culp, M.D., Rochester, Minn.
Urology

Lectures, symposia, clinicopathologic conferences, round-table luncheons, medical motion pictures and technical exhibits.

(All-inclusive registration fee—$20.00)

THE POSTCLINICAL TOUR TO MEXICO CITY, CUERNAVACA, TAXCO AND ACAPULCO

Leaving March 7 from New Orleans and returning March 18, 1958

For information concerning the Assembly meeting and the tour write Secretary, Room 103, 1430 Tulane Avenue, New Orleans 12, La.

Continued from page 74

NORTH CAROLINA

Dr. Eugene W. Loeser, Jr., was recently appointed to the faculty of the University of North Carolina School of Medicine.

Dr. E. C. Hamblen of the Duke University Medical School faculty has been invited to make an extensive lecture and teaching tour in South America.

Dr. Kenneth Brinkhous, head of the Department of Pathology at the University of North Carolina School of Medicine, has gone to Europe to attend a number of professional meetings.

Drs. John R. Ashe, Jr., Concord; William L. McLeod, Charlotte; Charles H. Peete, Jr., Durham, were recently certified by the American Board of Obstetrics and Gynecology.

Dr. J. Logan Irvin has recently assumed the chairmanship of the department of biochemistry and nutrition at the University of North Carolina School of Medicine, Chapel Hill.

OKLAHOMA

Dr. C. C. Gardner, Ponca City, was recently honored with the presentation of a Life Membership in the state organization.

Dr. Robert N. Saylor has recently assumed duties as medical officer in charge of the U. S. Public Health Service Indian Hospital in Lawton.

Dr. E. Malcom Stokes, Tulsa, recently took top honors at the Annual Physicians and Dentists Golf Tournament of the Tulsa County Medical Society.

TENNESSEE

Dr. James W. Culbertson has been appointed to the staff at the University of Tennessee as professor of medicine.

Dr. William H. L. Dornette will become professor of anesthesiology and head of the department, effective January 1, at the University of Tennessee.

Dr. Alvin J. Cummins was recently elected to membership in the Central Society for Clinical Research.

Dr. Harris D. Riley, Jr., an instructor in pediatrics at Vanderbilt School of Medicine, has resigned to accept the position of professor of pediatrics and chairman of the department of pediatrics at the University of Oklahoma School of Medicine, Oklahoma City, Oklahoma.

Dr. Elizabeth Rona, ORINS Special Training Division, spent the month of September in Europe, to deliver papers in France and Austria and to consult with other scientists in England and The Netherlands.

Dr. William G. Pollard, executive director of the Oak Ridge Institute of Nuclear Studies, was recently awarded an honorary Doctor of Divinity degree by Grinnell College, Grinnell, Iowa. Dr. Pollard is both a physicist and an Episcopal priest.

TEXAS

The University of Texas Postgraduate School of Medicine announces the Third Annual Postgraduate Course in Anesthesiology which will be given in the

Continued on page 83

for your Tension Headache patients...

to relieve both the pain and the distress Fiorinal acts against nervous tension, muscle spasm and pain—thus Fiorinal corrects the total mechanism involved/

Dose: 1 or 2 tablets, repeated P.r.n., up to six tablets per day/Each tablet contains: Sandoptal (Allylbarbituric Acid, N.F. X) 50 mg., Caffeine 40 mg., Acetylsalicylic Acid 200 mg., Acetophenetidin 130 mg.

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SANDOZ SANDOZ PHARMACEUTICALS
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Total Care OF THE PATIENT

Susceptibility to the effects of stress, physical or psychic, is aggravated by a poor nutritional state; resistance and recovery are promoted by enhanced nutrition.

In repair, use of energy and amino acids is increased with concomitant increase in demand for vitamins of the B complex. In many clinics, VITA-FOOD Brewers' Yeast is a routine, a vital aid to **total care** of the patient—emphasized anew as the rationally inclusive approach to ideal treatment.

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Samples and literature available on request

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EVERY WOMAN WHO SUFFERS IN THE MENOPAUSE DESERVES "PREMARIN"

widely used natural, oral estrogen

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New York, N.Y. • Montreal, Canada
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Continued from page 81

Texas Medical Center, Houston, Texas, February 19, 20 and 21, 1958.

Physicians, Dentists and Nurse Anesthetists may make application by writing to the University of Texas Postgraduate School of Medicine, Texas Medical Center, Houston 25, Texas.

Southern Medical Association announces with deep regret the recent death of Dr. James G. Flynn, of 2418 Travis Street, Houston 6, Texas.

Dr. Jacobus D. McCulley, Houston, has been elected president of the Texas Society of Anesthesiologists. Other officers include Dr. Milton M. Rosenzweig, San Antonio, as president-elect; Dr. David O. Johnson, Austin, vice-president; Dr. Randle J. Brady, Houston, secretary-treasurer; and Dr. Lawrence W. Schuhmacher, Houston, as program chairman.

Dr. Truman G. Blocker, Jr., Galveston, was recently elected president of the Texas Society of Plastic Surgeons. Other officers include Dr. Sidney Hardy, Houston, vice-president, and Dr. Steve R. Lewis, Galveston, as secretary-treasurer.

VIRGINIA

Dr. Drewery H. Mason, Ridgeway, was recently honored with a party commemorating his 50th year of service to Henry County.

Dr. Fred Maphis, Strasburg, was recently named vice-president of the Shenandoah County Tuberculosis Association.

Dr. Joseph T. Byrne, Richmond, was recently appointed medical director of the city service clinic at the Medical College of Virginia.

Dr. Allen T. Hawthorne, Winchester, was recently elected president of the Virginias Seniors.

Dr. E. G. Gill, Roanoke, was recently named a member of the Board of Governors from Virginia.

Dr. W. C. Caudill, Pearisburg, was recently named president of the United Fund drive of Giles County.

Dr. John T. Givens, Norfolk, was recently elected executive secretary of the National Medical Association.

WEST VIRGINIA

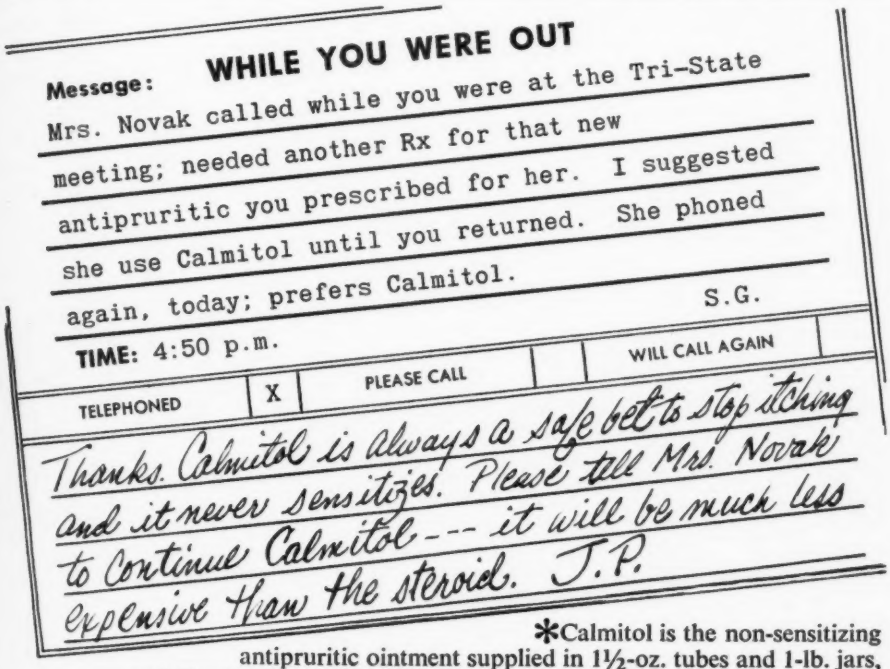
Dr. John F. McCuskey, Clarksburg, was recently elected president of the Alumni Association of West Virginia University School of Medicine. Other officers include Dr. Pat A. Tuckwiller, Charleston, vice-president, and Dr. Clark K. Sleeth, Morgantown, was re-elected secretary-treasurer.

Dr. E. W. McCauley, Bluefield, was recently elected president of the West Virginia Chapter of the Medical College of Virginia Alumni Association.

Dr. Ward Wylie, Mullens, has recently been named president-elect of the National Boxing Association.

Dr. Joseph T. Mallamo, Fairmont, recently won the annual medical golf tournament held in connection with the 90th annual meeting of the West Virginia State Medical Association.

Dr. Francis L. Coffey, Huntington, recently won the skeet and trap shooting tournament held in connection with the 90th annual meeting of the West Virginia State Medical Association.


Message: WHILE YOU WERE OUT
Mrs. Novak called while you were at the Tri-State
meeting; needed another Rx for that new
antipruritic you prescribed for her. I suggested
she use Calmitol until you returned. She phoned
again, today; prefers Calmitol.
S.G.
TIME: 4:50 p.m.
TELEPHONED
X
PLEASE CALL
WILL CALL AGAIN
Thanks. Calmitol is always a safe bet to stop itching
and it never sensitizes. Please tell Mrs. Novak
to continue Calmitol -- it will be much less
expensive than the steroid. J.P.

*Calmitol is the non-sensitizing antipruritic ointment supplied in 1½-oz. tubes and 1-lb. jars, and (liquid) 2-oz. bottles by THOS. LEEMING & CO., INC., New York 17.

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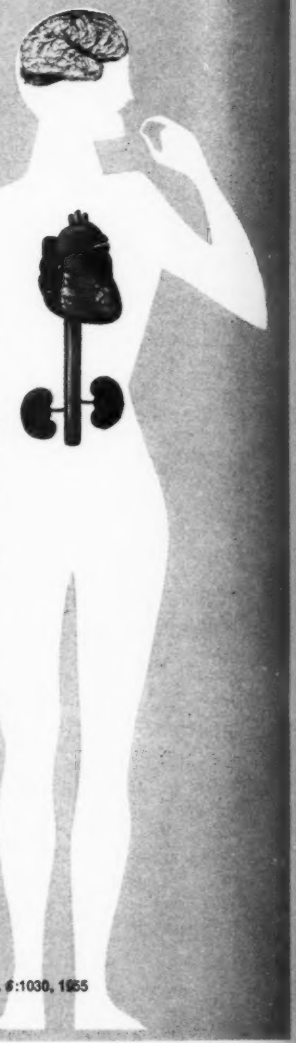
"ACTING IN CONCERT"†

to control

the entire syndrome of hypertension



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Cryptenamine dependably lowers blood pressure . . . increases cardiac output . . . improves cerebral and renal circulation and may arrest the degenerative processes which are accelerated by hypertensive vascular disease.

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When combined, cryptenamine and reserpine act synergistically, producing a far better therapeutic effect than when administered singly . . . and, successful therapy is generally attained with doses well below those producing side effects.

†Cohen, B. M.; Cross, E. B., and Johnson, W.: Am. Pract. & Digest Treat. 6:1030, 1955

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Cryptenamine (tannates) ..... 1.0 mg.
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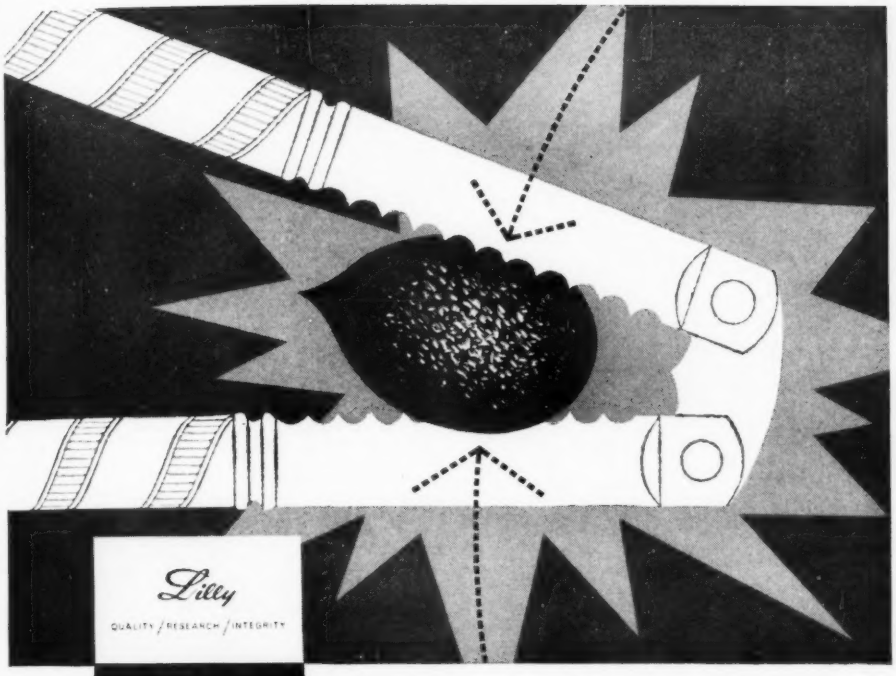
Bibliography. Orgain, E. S.: Postgrad. Med. *17*:318, 1955. Finnerty, F. A.: Am. J. Med. *17*:829, 1954. McCall, N. L.; Sass, D. K.; Wagstaff, C., and Cutler, J.: Obst. and Gynec. *6*:297, 1955. Cohen, B. M.: New York State J. Med. *55*:653, 1955. La Barbera, J. F.: Med. Rec. and Annals *50*:242, 1956. Voskian, J.; Assali, N. S., and Noll, L.: Surg., Gynec. and Obst. *102*:37, 1956. Crisp, W. E., and McCall, M. L.: Am. Pract. and Digest Treat. *7*:820, 1956. Finnerty, F. A.: Am. J. M. Sc. *229*:379, 1955.



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